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MSELENI JOINT DISEASE

A STUDY OF THE CLINICAL AND RADIOLOGICAL ASPECTS AND POSSIBLE MODES OF INHERITANCE

by
GILLIAN LOCKITCH

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University of Cape Town

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A STUDY OF

THE

CLINICAL AND RADIOLOGICAL ASPECTS

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by

Gillian Lockitch
M.B. Ch.B.

Submitted in fulfilment of the requirements for the degree of

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Faculty of Medicine

University of Cape Town

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For my husband, Bob, with whose
help and enthusiasm this work was begun,
and for Michael (5), Keith (3), and Amanda (1),
despite whose help and enthusiasm it was completed.

C O N T E N T S

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The photographs, with the exception of a few taken by the author, were taken by Mrs. U. Kache of Graphic Arts, C.S.I.R. The diagrams were drawn by the staff of the drawing office at the National Institute for Road Research.

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S U M M A R Y

Mseleni Joint Disease is a disabling polyarticular disorder occurring with a high prevalence in the Mseleni area of Northern Zululand. During the past three years the series of spidemiological, genealogical and clinico-radiological studies carried out in the Mseleni Joint Disease Project have resulted in:

1. the localisation of a high prevalence area and a neighbouring control or low prevalence area;
2. the identification of individuals affected by the disease and of families consisting of many such individuals;
3. the definition of the clinical and radiological aspects of the disease.

The description of these studies forms the subject of this thesis.

SECTION I

A chronological history of the early Mseleni studies is given to provide a background for the work of the author. This includes the first epidemiological survey and environmental studies as well as a clinical survey of affected individuals.

SECTION II

This section commences with a description of the status of the Mseleni Project at the time that the author was appointed as the medical member of the Mseleni Project team. The objectives of the project are defined, a hypothesis formulated and the planning of these studies described. The investigations described in this thesis are briefly reviewed and the methodology is described.

SECTION III

The geography of the area under study is described and the origins and life style of the people briefly presented. The results of the Mseleni studies are then presented and each study is discussed within the individual chapter.

III.2.1

Age specific prevalence rates derived from the 1973 enumeration of the high prevalence area and a prospective control area are detailed.

III.2.2

A study of the onset and symptoms of the disease in over 300 affected individuals is described. The findings on general examination of the Mseleni patients are presented.

III.2.3

The radiological features of the disease derived from a study of some 300 affected adults and children are described. The prevalence rates of various anomalies are compared with a sample from the population of the control area and with a random sample of Pretoria patients.

III.2.4

This chapter consists of a detailed genealogical study of five extended families from the high prevalence area. The possible modes of inheritance of Mseleni Joint Disease are considered.

III.2.5

The results of a study of 27 dwarfs from the affected area are presented and the relationship of the dwarfism to the Mseleni syndrome is discussed.

III.2.6

In this chapter a study of affected people living outside the high prevalence area is presented and its significance in relation to the disease aetiology is discussed.

III.2.7

A study of serogenetic markers in relation to radiological abnormalities among the population of the high prevalence area and a control area was carried out. Although the results of the analyses are incomplete and will be published later, the preliminary conclusions are mentioned.

Investigations carried out on four hospitalised patients with Mseleni Joint Disease are described. A study of twin pairs from the Mseleni population is briefly discussed.

SECTION IV

A survey of the literature on the hereditary epiphyseal dysplasias is presented.

SECTION V

This consists of a general discussion, a proposal for future studies on Mseleni Joint Disease and the conclusion which the author has drawn from the work described in this thesis.

LIST OF TABLES

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LIST OF FIGURES

A B B R E V I A T I O N S

MJD	:	Mseleni Joint Disease
MEDT	:	Multiple Epiphyseal Dysplasia tarda
SEDT	:	Spondylo-epiphyseal Dysplasia tarda
K-B	:	Kashin Beck
OA	:	Osteoarthrosis
MPS	:	Mucopolysaccharidosis
PsAch	:	Pseudo achondroplastic

I N T R O D U C T I O N

The research reported on in this thesis is part of an extensive large scale project to investigate what has come to be known as Mseleni Joint Disease hereafter referred to as MJD.

MJD is a painful and disabling joint disease which affects a large proportion of the indigenous population in a localised geographical area in northern Zululand. The MJD project was initiated with the purpose of determining the aetiology of this condition.

This project is a multidisciplinary one involving personnel and facilities from several different institutions (See acknowledgements) but the overall responsibility and control of the project is the concern of the Division of Medical Statistics and Epidemiology of the National Research Institute for Nutritional Diseases, an institute of the Medical Research Council of South Africa.

The project commenced with an epidemiological study to determine the prevalence rate of the disorder and to define the affected area. Studies of food and water supplies were also carried out. A pilot survey was carried out together with members of the Orthopaedic and Radiology Departments of the H.F. Verwoerd Hospital to establish the clinical and radiological features of the disease.

At the time that the data from the clinical survey became available, the author was appointed as the medical doctor on the Mseleni Project to work with the statisticians on the evaluation of the medical data and the

planning of future studies.

The first section of this thesis will therefore consist of a brief representation of the chronological history of the Mseleni project up to the point at which the author assumed responsibility for the medical aspects of the studies, while the remaining sections contain the original work of the author and a review of the relevant literature.

SECTION I :

A BRIEF REVIEW OF THE EARLY STUDIES ON THE MSELENI JOINT DISEASE PROJECT

SECTION I : A BRIEF REVIEW OF THE EARLY STUDIES OF THE MSELENI JOINT DISEASE PROJECT

In this introductory chapter a chronological history of the early work on the Mseleni project will be briefly presented, in order to provide a background and perspective for the original work of the author.

I.1 BACKGROUND TO THE PROJECT

In November 1969, the Head of the Division of Medical Statistics and Epidemiology was informed of an unusual disabling joint disease which apparently affected many of the indigenous population in a remote area of the Ubombo district of northern Zululand. (Figs. 1 and 2).

Femaleswere most commonly affected by the disease which was said to cause pain and stiffness of the hip-joints. Many women walked with an odd shuffling, stiff-hipped gait leaning heavily on two sticks.

The condition was apparently already known in the area when the missionaries arrived some fifty years before, and among the population was accepted as part of the pattern of life in Mseleni. The local name for the disease was "Isindulo or Unyonga" or"the disease affecting the joints"[156].

Interest was aroused by the estimated prevalence figure which seemed unusually high and by the apparent concentration of this disease in a small geographical area covering a few miles around the vicinity of the Mseleni Mission Hospital. (Fig. 3).

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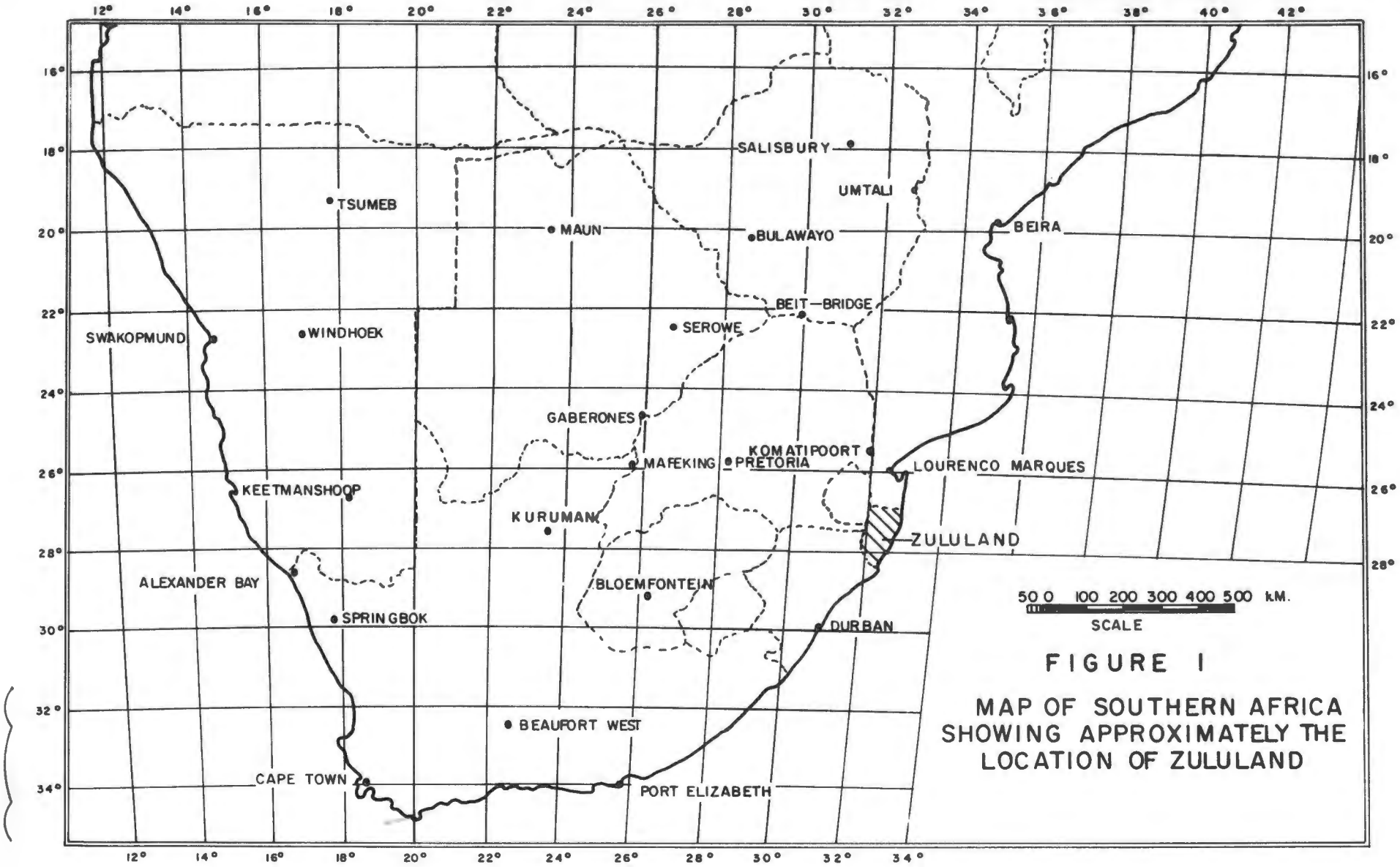

FIGURE 1

MAP OF SOUTHERN AFRICA SHOWING APPROXIMATELY THE LOCATION OF ZULULAND

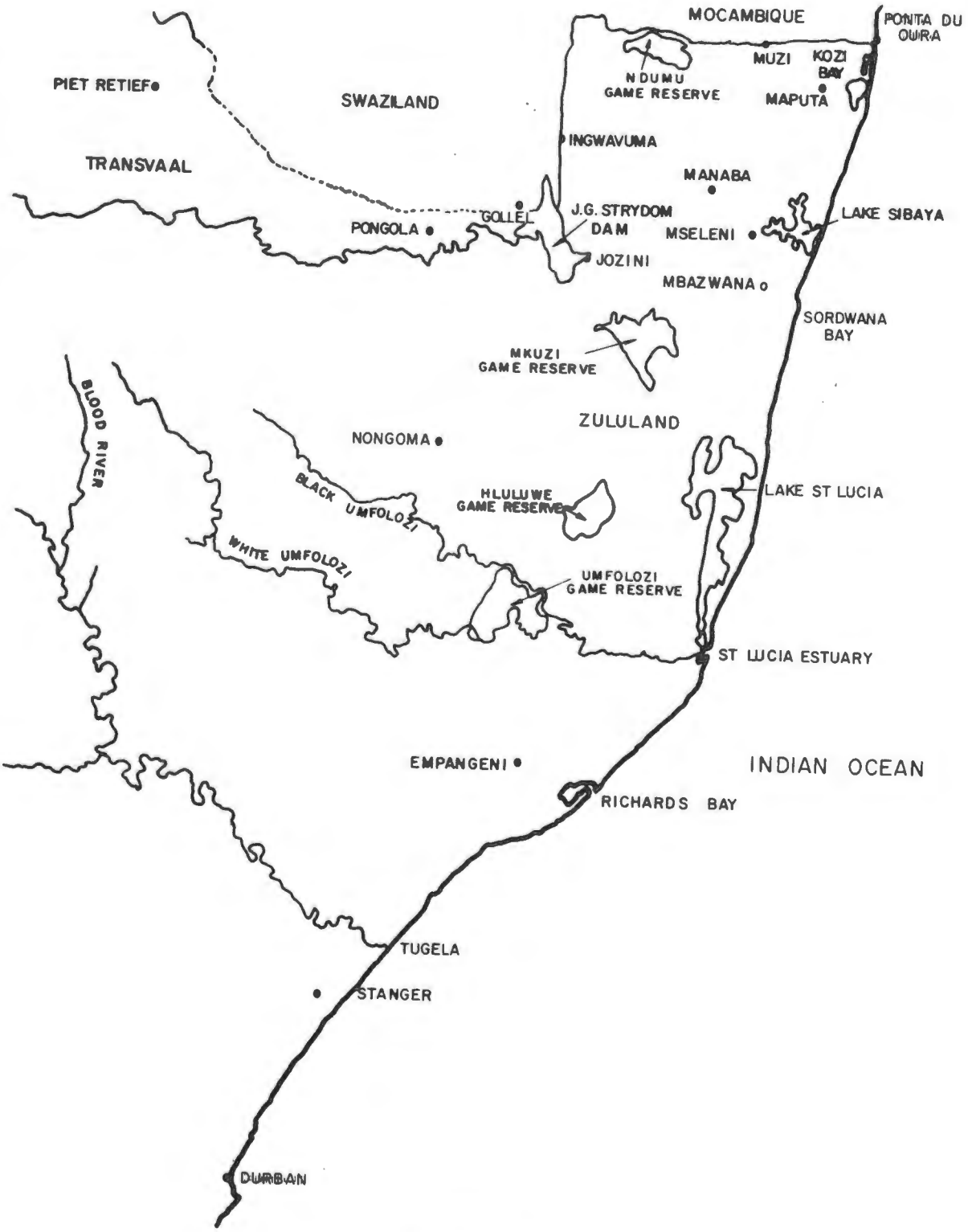

FIGURE 2

MAP OF ZULULAND TO SHOW LOCATION OF MSELENI AREA

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RG4-7172

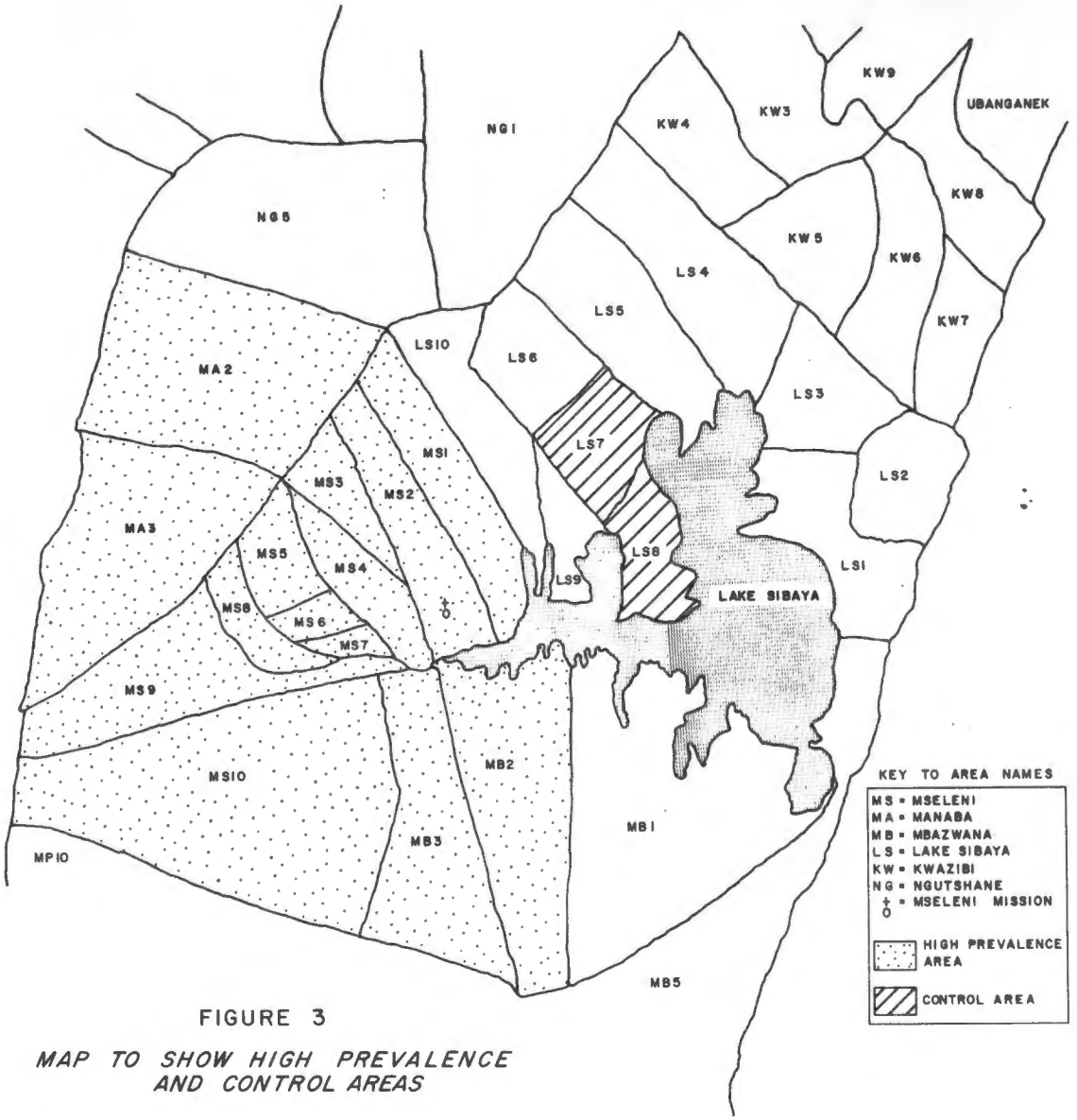

FIGURE 3

MAP TO SHOW HIGH PREVALENCE AND CONTROL AREAS

In order to obtain a rough estimate of the prevalence, the children at the Mseleni Mission School were interviewed. The eldest child of each family represented at the school was questioned, and on the basis of these answers it was estimated that the prevalence of the disorder probably exceeded 38% for the mothers and 4% of the fathers.

Since a prevalence figure of this magnitude indicated a very real problem, the Division of Medical Statistics and Epidemiology determined to make a large scale epidemiological investigation of the problem.

I.2 THE EPIDEMIOLOGICAL SURVEY

An epidemiological survey was carried out in order to:-

1. determine exact prevalence figures for the entire population;
2. determine whether there was a definite geographical area in which the disease occurred and, if so, to attempt to localise its boundaries;
3. attempt to find a control area for comparative purposes which from a geographical, climatic, botanical, socio-economical and dietary point of view was as similar as possible to the affected area, and yet was free from the disease.

A detailed description of the design, methods and results of the epidemiological survey has been described in a paper by Fellingham *et al.*[57] and only the conclusions will be mentioned here.

CONCLUSIONS FROM THE EPIDEMIOLOGICAL SURVEY

1. A consistently high prevalence rate for the disease among females was found throughout the Mseleni area, and in sections 2 and 3 of both Manaba and Mbazwana. This area will henceforth be referred to as the "affected area" or the "high prevalence area".

2. Prevalence rates for males over 10 years are probably not accurate due to the fact that many males of employment age leave the area to seek work in the towns.

3. Prevalence rates of 38,9% for females and 11,1% for males were recorded in the affected area. When only adults (over 18 years) were considered, the prevalence rates rose to 66% and 25% for females and males respectively. The prevalence rates increased with age from 2,3% in the 0 - 10 year age group to 70% in the 40 - 50 year group among females.

4. The age distribution of the female population was within the normal pattern for a rural Bantu area. The ratio of affected to unaffected women increased with age. This indicated that the disease did not shorten the lifespan of affected females.

5. It was found that the onset of symptoms might occur at any age but the peak frequency of onset for females was 40 - 50 years.

6. In order to investigate an apparent familial component to the disease, statistical tests for clustering of cases in kraals were carried out.

A kraal is the dwelling place of a man, his wives and their children. The test for clustering was designed to determine whether any kraals had a significantly higher or lower number of cases among men, women, children or the composite kraal population than would be expected from the prevalence rate for the particular group in the population as a whole. The tests revealed that there was a highly significant aggregation of cases observed when the children were tested but tests for clustering among men only, women only, or for the composite family revealed no clustering in kraals.

I.3 STUDIES OF FOOD AND WATER SUPPLY

(a) Food: Preliminary dietary surveys were made in the affected area and surrounding areas by Lubbe et al.[112] During these surveys no striking differences in dietary patterns were observed between the affected and control areas although there seemed to be a greater food shortage and lower animal protein intake in the affected area. Diet in both areasconsisted mainly of maize, sweet potato, melons and calabashes, cowpeas, peanuts, wild fruit and vegetables. A few families kept cattle and goats but they did not usually serve as a source of food. Most families owned only a few chickens.

A popular drink in the area is "injemane" or ubusulu" - palm wine brewed by the menfolk from the Lala and Sundu palms. This is the only form of work for most of the men who are not employed in towns outside the area.

(b) Water samples from sources used by people from the affected and

surrounding areas were analysed over a period of a year. Detailed chemical analyses indicated that on the whole the water was of good chemical quality with little organic pollution present.

Analyses for the following substances were carried out - cadmium, chloride, chrome, copper, fluoride, iron, lead, manganese, sulphate, selenium, zinc, calcium, nitrate and magnesium. The amounts were compared with standards laid down by the World Health Organization[181] and the United States Public Health Service.[169] No unusual accumulation of heavy metals was found with the exception of iron which exceeded the permissible amounts in the control area but not in the affected area.

Statistical tests indicated that sulphate, magnesium and silica differed between the affected and control areas at varying times while aluminium differed over one period. Although it was felt that these parameters merited further investigation, no definite leads as to the aetiology of MJD were found.

I.4 THE PILOT CLINICAL SURVEY

The next major line of investigation was to attempt to define clinically, biochemically and radiologically the components or entities which caused the symptoms of the disease. Accordingly about 200 affected people were examined during a pilot survey intended as a preliminary study to aid the planning of more detailed studies. Details of the planning, execution and results of the clinical survey are available in a publication by Lockitch *et al.*[109], while the details of the biochemical study are contained in a publication by Burger *et al.*[29].

The results of this survey are summarised below:-

(a) History: The histories given by the patients followed a fairly standard pattern. The first symptom was always pain in the large joints of the lower limbs, i.e. hips, knees or ankles. The onset of the pain was gradual and unassociated with an acute illness. Increasing pain and stiffness resulted in decreasing mobility so that many people needed to lean on sticks in order to walk.

The hip joint was most commonly affected, followed by knees and ankles, while wrists, shoulders and elbows were less commonly sources of pain.

Most patients gave a positive family history of joint disease.

(b) Examination: The people were generally short and thin but evidence of gross malnutrition was not seen. Some adults were markedly dwarfed (130 cm and less) while others were of normal height or relatively tall.

A marked lumbar lordosis was commonly seen. No indication of mental or sexual retardation was present in these patients.

Examination of the affected joints in the adult patients revealed signs of degenerative arthroses of varying severity. Marked degrees of osteoarthrosis were seen even in young adults. Characteristically, multiple joints appeared to be affected and signs of severe degenerative joint disease were seen in even the elbows and shoulders in a few patients.

The children, in general, had no gross symptoms apart from

joint pain, and in a few cases, decreased range of flexion and internal rotation of the hips or genu valgum.

In both adults and children, examination of other systems revealed no constant abnormality.

The impression at the close of the clinical survey was that the Mseleni problem was that of a generalised or multiplex osteoarthrosis, often of premature onset in fairly young adults.

A possible lead as to the cause of this osteoarthrosis was only obtained when the radiographs of the survey patients were screened.

(c) Radiological examination: The radiological abnormalities of the joints were classified into several broad groups. In the younger patients, findings varied from irregularity of outline and density of the joint surface to gross deformities of the joint epiphysis. This joint surface irregularity was thought to be a form of epiphyseal dysplasia.

A second group showed epiphyseal dysplasia with the changes of early degenerative joint disease. In a third group the findings were those of a severe osteoarthrosis affecting multiple joints. The osteoarthrosis was in many cases so severe that no underlying or predisposing abnormality could be detected. In many cases mild degrees of protrusio acetabulae were noted while in a few cases very gross degrees of acetabular protrusion were seen.

The hip was always affected while knees, ankles, shoulders,

wrists and the small joints of the hand were affected in many, but not all of the patients. A small group showed gross deformities of the wrist with hyperplasia or hypoplasia of the distal end of the radius and/or ulna, and deformed carpal bones. In a number of the hand radiographs examined, brachymetacarpaly was present.

The spine, skull and feet were not studied except in one or two cases where spinal radiographs were specifically requested by the examining doctor. These revealed osteoarthritic changes. The thoracic radiographs revealed pulmonary tuberculosis in 3 cases while in a few pelvic radiographs, bladder calcification suggestive of bilharzia was present.

(d) Biochemistry: Parameters that were measured included the haematocrit, erythrocyte sedimentation rate, alkaline phosphatase, serum calcium, phosphorus, magnesium, sodium, potassium, chloride, bicarbonate, total protein and protein electrophoresis. A test for Rheumatoid factor was also performed. The only constant abnormalities which were found were a slightly decreased serum alkaline phosphatase and slightly low inorganic phosphate and calcium phosphate products.

It was felt that these parameters merited further investigation and a series of studies were to be undertaken by the Division of Biochemistry.

CONCLUSION FROM THE CLINICAL SURVEY

The feeling at this stage was that the mechanism causing MJD was an abnormality of bone development which produced anatomical joint abnormalities with subsequent development of severe degenerative joint disease of premature onset.

The factor which distorted bone development could be either hereditary or environmental in origin. Such environmental factors could include toxins, dietary deficiencies or dietary excesses or chronic infections.

While the investigation of possible environmental factors and of the biochemistry of the disorder were to be continued by co-workers, the initiation and carrying out of an intensive investigation into the familial and hereditary aspects, and the further clinical and radiological investigation of affected people was the responsibility of the author.

The remainder of this thesis is concerned with the aims, methods, results and conclusion of this aspect of the survey.

S E C T I O N II

THE PLANNING OF THE MSELENI STUDIES

II.1 THE STATUS AT THE END OF THE CLINICAL SURVEY

At the time that the author commenced work on the research programme reported on in this thesis, the clinical survey had been carried out, the orthopaedic and biochemical results were being statistically analysed and the screening of the radiographs from the survey patients was in progress. The general conclusion derived from the survey was that the adult patient with MJD was affected by a severe disabling form of osteoarthrosis involving multiple joints but particularly the hips and with premature onset in fairly young adults.

It was obvious that with a high prevalence rate of generalised osteothrosis among a population concentrated in a localised geographical area a potent predisposing factor had to be operative.

When the results of the radiographs from the clinical survey became available it appeared that such a predisposing factor had been found. While the radiographs in the older patients confirmed the clinical diagnosis of a polyarticular osteoarthrosis, the appearance of the joints in the children was that of an epiphyseal dysplasia.

The joint epiphyses were small, deformed and irregular in shape and density. Carpal and tarsal bones were misshapen, while the distal ends of radius and ulna in several pateints were deformed and of abnormal length. When the radiological findings were tabulated against age it was found that while the epiphyseal abnormalities predominated in the younger patients, osteoarthrosis was found in the older patients, a third group of patients, mainly young adults showed epiphyseal dysplasia with early

degenerative changes superimposed. This suggested that the primary abnormality was an epiphyseal dysplasia which predisposed to the development of osteoarthrosis.

It was known that a number of conditions could produce this appearance in the joints[55]. These included congenital hypothyroidism, the osteochondritides,certain of the mucopolysaccharidoses, in particular Morquio's disease or MPS IV and the hereditary bone dysplasias of the multiple epiphyseal dysplasia and spondylo-epiphyseal dysplasia group.

Congenital hypothyroidism was excluded on clinical grounds. The osteochondritides do not commonly involve multiple joints. The patients did not resemble any of the recognised mucopolysaccharidoses and were obviously not cases of Morquio's disease.

The localisation of pathology to the skeletal system, specifically to the joints, the pattern of symmetrical multiple joint involvement together with the apparent familial occurrence of MJD seemed to favour the diagnosis of a hereditary bone dysplasia, and the epiphyseal abnormalities were characteristic of those seen in the multiple epiphyseal dysplasias. Furthermore, it was known that the epiphyseal dysplasia predisposed to the development of premature osteoarthrosis.

While available evidence thus favoured the diagnosis of a form of multiple epiphyseal dysplasia, a well recognised group of genetic entities, the environmental studies had as yet failed to produce any definite lead. It was accordingly decided that resources should be concentrated on investigating the genetic aspects of MJD.

As the medical member of the Mseleni team it fell to the author to investigate the possibility of a hereditary cause for the disease.

II.2. FORMULATION OF A HYPOTHESIS

Objectives

The prime objective of the MJD project was to determine the basic aetiological factor which causesthe disease. In the Genetic Studies this was approached in two ways:

1. The definition of the clinical, radiological and biochemical features of MJD to determine whether it resembled any known well-defined disorders.

2. The investigation of possible modes of inheritance of MJD. The investigations were to be designed so that these two aspects would be studied concurrently.

The first step in the design of the studies was the formulation of a hypothesis. From the earlier studies several significant facts were known:

(a) The end stage of the disease was a form of osteoarthrosis.

(b) Young patients appeared to have a form of epiphyseal dysplasia.

(c) Both males and females were affected by the disease, although more females appeared to be affected.

(d) All the affected children thus far seen had at least one affected parent.

This suggested that the original joint abnormality was epiphyseal dysplasia and that osteoarthrosis was superimposed on this. A further implication was that if a genetic mechanism were implicated, the gene

would probably be a dominant.

Since it is easy by invoking variation in penetrance and expressivity to make almost any pattern of disease occurrence fit a genetic model, a simple and definite genetic hypothesis was formulated, which could clearly and easily be proved or disproved.

MSELENI JOINT DISEASE IS CAUSED BY A HEREDITARY EPIPHYSEAL DYSPLASIA WHICH RESULTS IN DEFORMED JOINTS AND PREDISPOSES TO THE DEVELOPMENT OF OSTEOARTHROSIS IN THESE JOINTS: IT IS INHERITED BY A SIMPLE DOMINANT GENE WHICH SHOWS COMPLETE PENETRANCE BUT VARYING EXPRESSIVITY: THE SYMPTOMATOLOGY IS MODIFIED BY SIMPLE ENVIRONMENTAL FACTORS WHICH PRODUCE SYMPTOMS MORE COMMONLY IN FEMALES: THESE FACTORS COULD BE THE STRESSES AND HORMONAL EFFECTS OF CHILDBIRTH AND PREGNANCY, AND THE EFFECT OF HARD LABOUR IN THE FIELDS ON ABNORMAL JOINTS.

The studies described in this thesis were designed to show the validity or otherwise of this hypothesis.

II.3. A BRIEF REVIEW OF THE STUDIES THAT WERE UNDERTAKEN

In order to amplify the statements set out in the hypothesis, and to try to answer some of the questions formulated earlier, a number of surveys were instituted. These are briefly described below:

1. Re-enumeration of the population and establishment of a population data base

The population of the area where a high prevalence of MJD was present and of a control area was fully enumerated on a kraal-by-kraal basis. Genealogical, epidemiological and clinical data was obtained.

Since it was realised that long-term follow-up studies would probably prove of great value, the above studies were designed and the work carried out in such a way as to provide a population baseline and framework for future studies. The methods used and the type of information available are discussed under the section on Methodology. The prevalence figures are discussed on pages 43 to 52.

2. A study of the onset and effect of MJD in affected people

Every affected individual listed in the enumeration was supposed to be interviewed by a fieldworker regarding the onset of his joint disease and the effect on daily living. Unless personally questioned by the fieldworker an affected person was not included in this study. The findings are presented on pages 54 to 63.

3. The findings on examination of affected people

This section is based on the examination of affected adults and children during the course of the genealogical studies. The findings are described on pages 64 to 67.

4. The radiological abnormalities in MJD

Approximately 300 people suffering from MJD were studied. Most of these were members of 5 major genealogies selected for study on the basis of one or more dwarf propositi. Some were members of family units drawn randomly from the population of the affected area. Radiographs of hips, knees, ankles, feet, hands and wrists, elbows and lumbo-sacral spine were examined. The results are presented on pages 69 to 103.

5. A study of dwarfed individuals from the high prevalence area

A number of extremely stunted individuals were noticed by the author while visiting kraals in Mseleni and Manaba. These people were studied in detail in order to determine the relationship of the dwarfism to MJD. These results are presented on pages 155 to 189.

6. A study of randomly selected family units

Since the families studied in the genealogical survey were selected specifically on a propositus bases, it was felt that a further study should be made of randomly selected families which would be representative of the population and from whom population inferences could be made. The results of this study are not completed but the radiological findings among the parents are discussed in the section III.2.3. The radiological results

are tabulated and presented on pages 90 to 99.

7. A study of 5 major genealogies

A study of affected families from 5 of the major clans in the Mseleni and Manaba areas was carried out to determine the relationship of affected families and affected individuals within each family to one another. Inter- and intrafamilial variation in disease pattern and possible modes of inheritance were looked for. The results are presented on pages 113 to 153.

8. A study of affected people living outside the high prevalence area

An area where the prevalent rate for MJD was thought to be low and yet which was within an hour's drive from Mseleni was enumerated. The low prevalence rate was confirmed. People who were classified as affected were examined radiologically and questioned regarding possible connections with the high prevalence area. The results are presented on pages 119 to 204.

9. The serogenetic survey

In order to obtain an idea of the population dynamics of the affected area, studies of serogenetic markers were carried out in the Mseleni/ Manaba and a control population. Blood and saliva was collected for the estimation of genetic markers in thirteen systems and hands, knee and pelvic radiographs were taken to establish a radiological incidence and diagnosis. The statistical analysis is still in process and the results are therefore not available for inclusion in this thesis.

II.4 METHODOLOGY

II.4.1 ESTABLISHMENT OF A POPULATION FRAMEWORK AND CREATION OF A DATA BASE

The original enumeration of the population of the affected area had been carried out three years previously and parts of the area had been enumerated on a sampling basis. The original census had, in addition, not been designed to elucidate relationships between enumerated individuals and families. Furthermore, at the beginning of 1973 a complete renumbering of the kraals had been carried out by the Health Department as many old kraals had been destroyed or moved. It was decided, therefore, to carry out a complete re-enumeration of the population with whom we would be working. This would:

1. Provide an exact base-line population for the enumeration period.
2. Provide a framework for sampling procedures for further investigations.
3. Provide a basis for comparison with future epidemiological studies, and for the obtaining of accurate demographic data.
4. Enable comparisons to be made with the data obtained from the first census to see whether:

   (a) affected people had worsened or improved;

   (b) asymptomatic people had developed disease;

   (c) estimates of crude birth and death rates, of age at marriage, and of indices of migration could be ascertained.

5. Provide data for genealogical and isonomy studies.

II.4.2 DELINEATION OF THE POPULATION TO BE STUDIED

Based on the results of the original enumeration of Mseleni and surrounding area[57], two population groups were defined.

High prevalence group: The inhabitants of the kraals situated within the areas of high disease prevalence i.e. Mseleni sections 1 - 10, Manaba sections 2 and 3 and Mbazwana sections 2 and 3.

Control group: The inhabitants of an area away from the high prevalence area, in which the prevalence rate was expected to be low. This area comprised Lake Sibaya sections 7 and 8. The two areas may be seen in Fig. 3. (The boundaries of areas and sections were, as will be described, arbitrarily defined by the State Health Department to aid in the control of their public health work, and these boundaries have no specific geographical or other significance. It was found convenient to define our groups initially by these boundaries and it will be indicated later how these prevalence groups relate to actual prevalence rates).

II.4.3 CENSUS METHODS

A kraal (the collection of huts inhabited by a man and his immediate family) was selected as the basic unit for the enumeration. A census form was designed to be completed for every kraal in the areas selected. The kraal was located by area, section and kraal number, the name of the kraal head, and of the chief and induna (headman) under whose jurisdiction

the kraal members were. Each member of the family unit was listed and given a sequential number. Members of the immediate family who were living or working elsewhere, or who had died, were indicated on the form. The relationship of each individual in the family was indicated. Thus a unique 11 digit population number was created for every person. It consisted of area code, section number, kraal number and number within the kraal. Deceased people and those living elsewhere were indicated by a particular code. This information was used to form the basis of a record for every individual in the population, and stored on disc for data processing purposes. The age and sex of each person was recorded and whether he or she had joint disease symptoms or was dwarfed. Concurrently with the enumeration, other information was sought:

A family history form (appendix 1) was designed to obtain detailed family information to enable the drawing up of pedigrees for each family, and the eventual compilation of composite genealogies. Thus the information obtained from a family ideally included names of the parents and grandparents, children and grandchildren, uncles, aunts and cousins as well as half sibs of the husband and all his wives. Subjects were also questioned as to the whereabouts of these relatives, estimated ages, and whether or not they were thought to be affected by Mseleni joint disease.

The genealogies were drawn on box cards to be later checked for accuracy and linkages, and the names of all people listed were cross-indexed by surname and maiden name where applicable (Fig. 4).

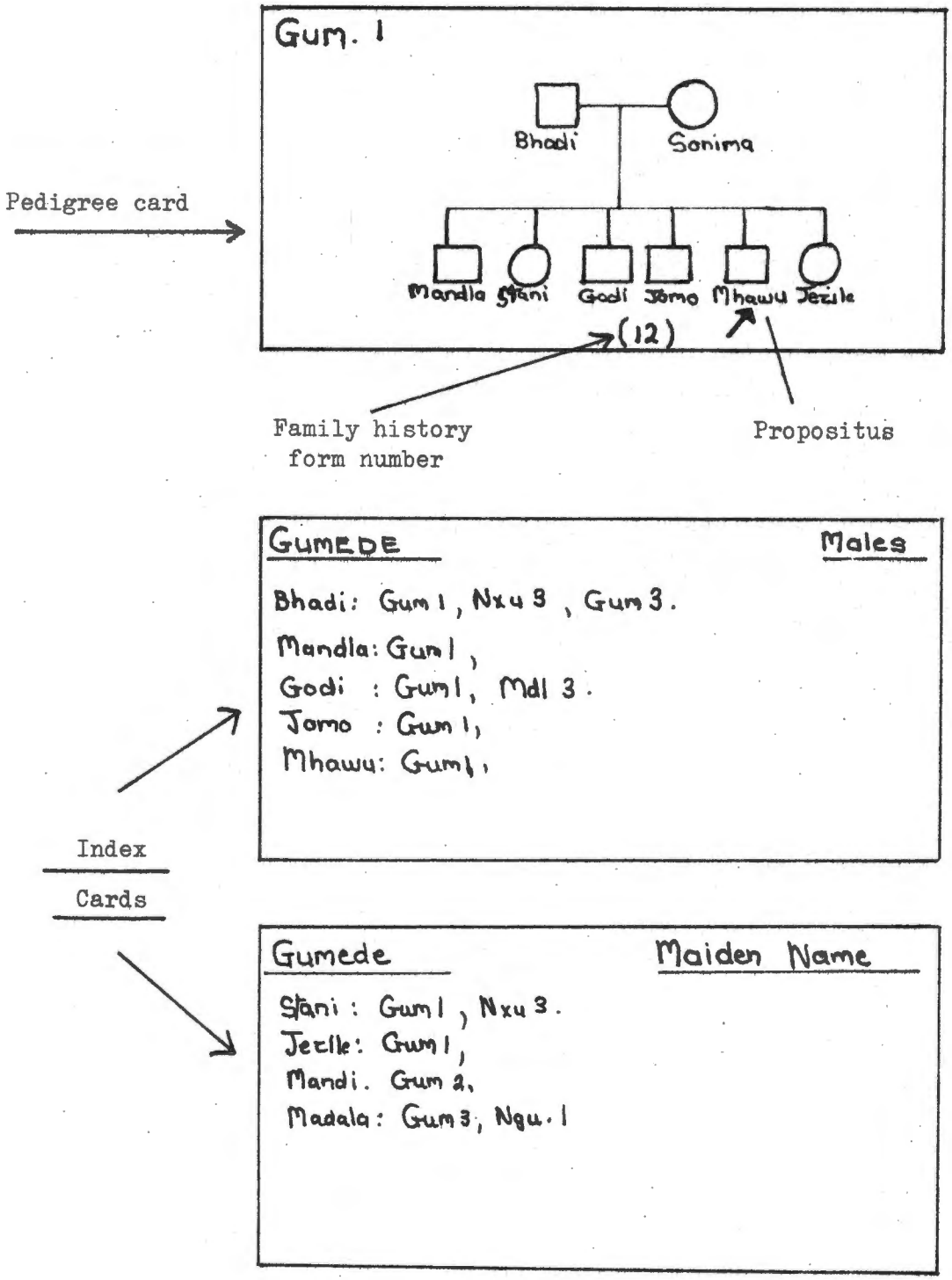

Figure 4 : Card index system for family history forms.

A symptom form (appendix 2) was designed to obtain information about the onset and development of the disease. The information requested included age, period of onset, relation of symptoms to the period of reproduction in the case of females, the number and distribution of joints affected and associated systemic illness or symptoms at the time of onset of joint symptoms. The subject was also asked whether any relatives were dwarfed and whether there were any affected relatives living away from the area. A separate symptom form was completed for every affected person enumerated who was available to be interviewed in person by one of the fieldworkers. The information was coded onto punch cards to be added to the subject's record.

II.4.4 COLLECTION AND PROCESSING OF THE DATA

This aspect of the project is summarised in a flow chart in Fig. 5

1. The census, family history and symptom data: Two health assistants seconded from the Department of Health at Jozini, interviewed all the subjects. The forms were then processed in Pretoria, where the data was coded and punched onto cards and where the family unit pedigrees were drawn onto box cards and indexed by the clerical staff of the Division of Medical Statistics and Epidemiology. The collation of the family unit pedigrees and the compilation of the extended genealogies was carried out by the author.

2. The radiographs: These were taken and developed at the Mseleni Mission Hospital mainly by a radiographer appointed specifically for this study. Part of the earlier work was done by the hospital radiographer.

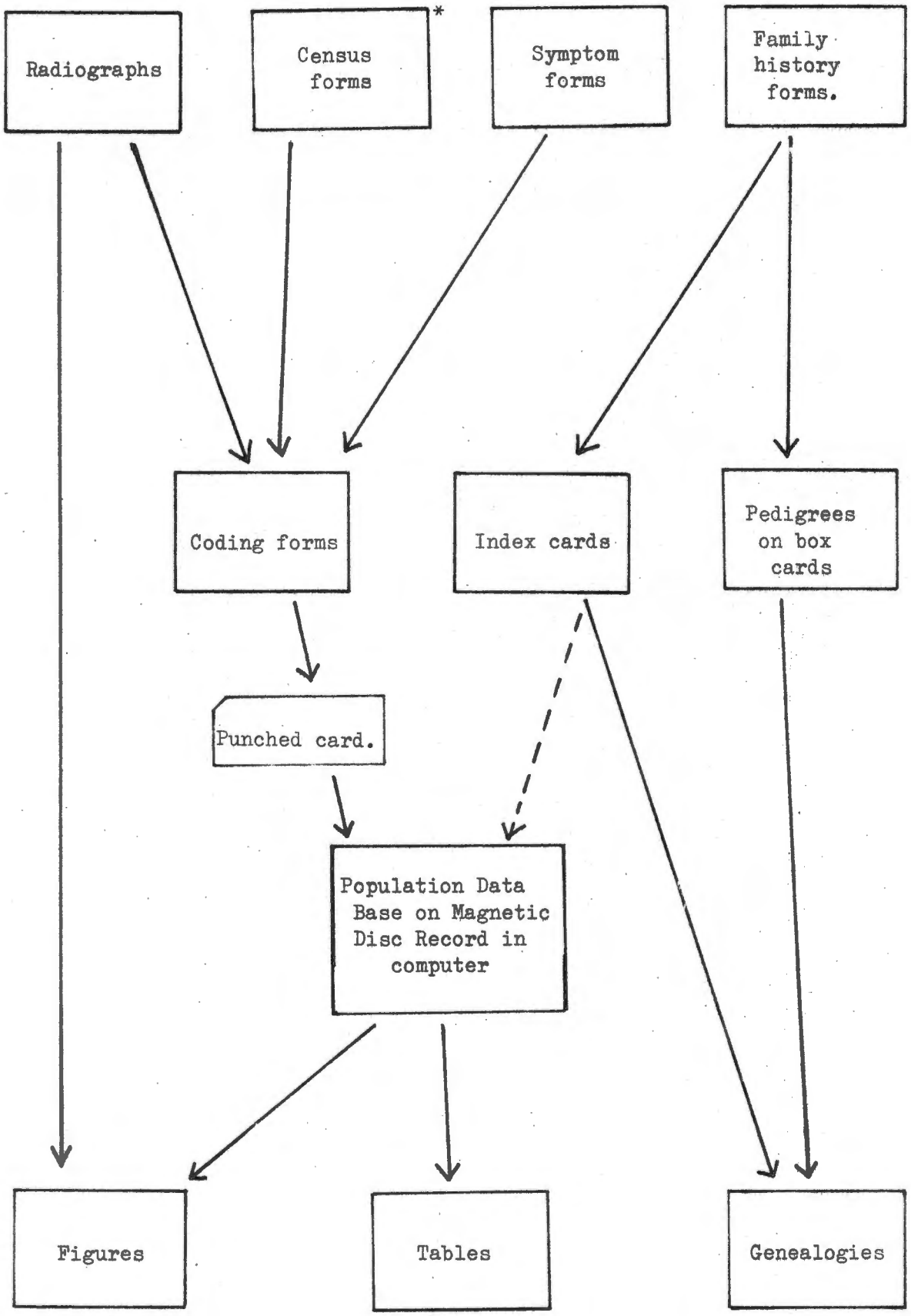

FIGURE 5 : Diagram illustrating Data Capture and Retrieval.

The films were then sent to Pretoria where the author examined them and coded the findings.

3. Clinical data as well as clarification and confirmation of the other data was directly obtained by the author from the patients with the aid of the health assistants and nurses from the hospital who helped with interpretation between Zulu and English.

4. The punch card data was then transferred to magnetic disc files. The major part of the computer programming and statistical analysis was done by C.D. Elphinstone of the Division of Medical Statistics and Epidemiology. Part of the programming was carried out by A. Buitendag of the same division. The prevalence figures tabulated in the radiological section were obtained from programmes written by M. Soltynski and F. du Toit of I.B.M. as were those in section III.2.2.

The data was processed mainly on the I.B.M. System 360 Model 65 of the C.S.I.R. computing centre with part of the work being done on the I.B.M. System 360 Model 50 at the University of Pretoria.

The population data base

The basic population data set comprises a record of every person listed in the enumeration, identified by a unique population number, by name, age and sex and by disease status (affected or unaffected as recorded on a basis of symptoms only). To this will be added where applicable for each person, a record of the radiological findings and of the clinical symptoms or other data obtained.

II.4.5 SELECTION OF SUBJECTS FOR DETAILED STUDIES

People were selected for the studies in one of two ways:

1. By random sample.
2. By propositus method.

A random sample of people for study was selected wherever the data obtained was required to be representative of the population at large. This method of sampling was used in the multiple family unit studies, the study of radiological prevalence rates in a control population group and in the study of serogenetic markers.

Selection of families for extended genealogical studies was made by the propositus method. A number of severely dwarfed individuals with MJD who had been radiologically examined, were initially selected as propositi, and their original family unit pedigrees (drawn on box cards as described earlier) were studied.

When those pedigrees were collated, 12 of the dwarfs were found to be related to at least one of the other dwarfs. Each family to which 2 or more dwarfs belonged was selected for fuller investigation and extended pedigree charts were compiled. Finally 5 of these extended families were selected for detailed radiological study. These were the Maphanga, Ngubane, Mdletshe-Manukuza, Sibiya-Nxumalo and Gumede families.

Since a few asymptomatic individuals had been found to have radiological evidence of joint abnormality, for the purpose of the investiga-

tions, each person was categorised under the phenotype "affected" or "unaffected" on the basis of radiological evidence. An "affected" person was one who had evidence of established osteoarthritis or epiphyseal dysplasia in the hip joint, or in at least two other types of joints. Those persons with short metacarpals or metacarpals, or other anomalies as isolated abnormalities were initially regarded as possibly affected and it was hoped that these studies would enable reclassification of these problem cases into the "affected" or "unaffected" category.

Sampling problems

A far greater resistance was noted among the men, than among women, when requested to attend the hospital for radiological examination or to donate blood. On several occasions a man would be completely agreeable for his wives and children to participate in a study, but would refuse to participate himself. It is possible that bias would have crept in to the samples, with affected males who had mild joint pains refusing to enter the sample for fear of hospitalisation.

The second enumeration was carried out after members of the Mseleni Project team had carried out a number of surveys which on occasion required blood samples. It is possible that a fear of being required to give blood may have led to affected people of either sex denying any symptoms.

A second problem in sampling was the number of men who were working away from the area. Whether affected men would be more likely to move away in the hope that their pains would disappear, is not known. However, the greater mobility among men compared to the women, who tend to stay

at home could make this another source of bias in sampling.

SECTION III

THE CLINICAL AND RADIOLOGICAL FEATURES OF MSELENI JOINT DISEASE WITH REFERENCE TO THE INDIVIDUAL, THE FAMILY AND THE POPULATION

III.1 INTRODUCTION

III.1.1 THE GEOGRAPHY OF THE REGION[177]

The area where MJD is prevalent is situated in the Ubombo district of Northern Zululand. Zululand occupies the north-eastern section of the Province of Natal. It is bordered on the north by Mocambique, on the south and south-west by the Buffalo and Tugela rivers, on the east by the Indian Ocean and on the west by Swaziland. (See Figs.1 and 2).

This region falls in the coastal belt of subtropical forest or dense evergreen bush. The soil is porous and sandy with few organic elements. The climate is warm. The July mean temperature is usually over 15°C (60°F) while the summers are hot with the January mean maximum temperature usually exceeding 29°C (or 85°F).

The area has a predominantly summer rainfall but in general about 30% of the mean annual rainfall of 40" is received in the winter half year. Wild life is plentiful and is protected in numerous parks and game reserves. Hippopotamuses, crocodiles and water fowl abound in the numerous fresh water pans.

Northern Zululand is endemic for malaria, and the tsetse fly formerly infested Zululand as far south as the Umfolozi River. The population density in 1967 in Northern Zululand was 50 people to the square mile.

The Mseleni area is about 13 x 18 km, situated in the Ubombo District of Northern Zululand. It lies on the western shore of Lake Sibaya approxi-

mately midway between St. Lucia in the South, and Kosi Bay in the north, about 50 km from the South African/Mocambique border. (See Fig. 2).

State Health Inspectors working on a malaria eradication campaign have arbitrarily divided the region into area, e.g. Mseleni, Manaba, Mpakatini, Mbazwane and Lake Sibaya. Each area has been divided into sections and every kraal in each sector has been numbered (Fig. 3).

III.1.2 THE PEOPLE OF THE REGION[27, 28, 140].

The Negroes of South Africa belong to four main sections or families: the Nguni, the Sotha, the Venda and the Tonga families, most of whom probably arrived in this region from the north during the past 1 000 years.

The population of the Mseleni area of the Ubombo District of northern Zululand is largely descended from the Nguni and the Tonga division of the Tsonga peoples.

Some 150 years ago when Shaka came to power there were over 50 independent clans, many with subordinate subclans living in Zululand. A clan is defined as a collection of 50 - 500 families whose origins may be traced through 4 - 8 generations in the male line to a common father, whose living representative rules as clan chieftan.

All members of a clan share a common clan-name or isibongo. A subclan is a section of a clan, the members of whom are also descended from a single ancestor and have one isibongo but which does not have an

Fig. 6: A typical kraal in the Mseleni area

Fig. 7: A woman affected by Mseleni Joint Disease

Fig. 8: The lala palm — source of palm wine

Fig. 9: Woman carrying water to the kraal

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independent chief and is subordinate to the clan chief.

Before the time of Shaka, Northern Zululand was inhabited by the Tembe tribe, members of the Tonga family who mainly occupied the land extending north from Delagoa Bay along the Portuguese East African coast. During the wars of Shaka, a continuous stream of refugees moved north to live among the Tembe and the distinctive Tonga character and language became greatly modified, taking on more and more Nguni characteristics (of Zulu type).

Early this century, around 1912, a few missionaries settled in Mseleni and founded the Mseleni Mission Station which to-day embraces a hospital, serving as a training centre for auxiliary nurses. A western-ising influence has since then become apparent around the mission. The completion of the railway line from Durban to Gollel in 1927 opened the nearby areas to development by Europeans, but this had little effect on the Mseleni area. The people live in grass huts, grouped into kraals, (See Fig. 6) each kraal being the homestead of a family, consisting of a man, his several wives and their children. Each wife inhabits a separate hut together with her children, and the husband usually takes his meals with each wife in turn. In Fig. 7 a woman affected by MJD is shown.

The husband is responsible for the clearing of the dwelling site and the building of the huts. To him, in areas where lala wine is brewed, also falls the task of collecting the sap of the lala palm (See Fig. 8). The women spend much of the morning gathering food and preparing the evening meal which bubbles quietly in the heavy iron pots throughout the

afternoon. They are responsible for the clearing and ploughing of the fields, the planting, cultivation and harvesting of the crops. Many kraals are situated deep into the bush far from the sand "main roads" and from the water supply. The women carry heavy buckets on their heads for long distances bringing water from the waterholes to the fields (Fig. 9).

A group of kraals will fall under the jurisdiction of a headman who in turn is responsible to a district headman or umnumzana. The district headman are controlled by an induna who reports to the chief.

To-day the people mostly wear western dress and many men move away to the towns to work. Some women come to the Mission Hospital for their confinements, and a baby clinic at the hospital is flourishing. Yet many births still take place in the dim interior of a hut in the presence of the old women of the kraal, and many children are brought to the hospital desperately ill only when the witchdoctor's treatment has failed.

Employment and movement in and out of the area.

A few men from the area are employed at the Mission where they assist with building, plumbing and general maintenance. Apart from this, there is no other source of income for the local families, therefore, among the present day population, most of the men leave the area to work in the larger towns and cities such as Empangeni, Stanger, Durban or in the forestry industry at Mbazwana. Although there are Recruiting Corporations hiring men for the gold mines, at Maputa, Ingwavuma and Gollel, few people from the Mseleni area go to the mines. They prefer

to work in the sugar mills and in the forestry industry which started up about 1958. This movement of men to the towns is probably a comparatively recent phenomenon of the last ten to twenty years or so according to local sources.

Other characteristics of the population which affected the studies:

1. Degree of isolation: The population of the affected area cannot at the present time be clearly separated from the surrounding population either by descent, by geographical or marriage boundaries, or by religious or cultural differences. While it is not known to what extent folk favour marriage to people in close proximity, though most marriages are contracted with people from the same area, marriages at a distance definitely do occur. During the original enumeration, when asked how long they had lived in the area, almost all the people replied that they had lived there all their lives.

2. Records: There are no written records of births and deaths for the bulk of the population, and few subjects interviewed could remember with accuracy further back than a grandparent. The compilation of genealogies was therefore an extremely laborious task and it was soon realised that identification of a founder population would be impossible.

3. Ages: Ages are unknown among most of the population and all ages recorded are estimates except among the very young children born at the Mission Hospital.

4. Naming system: The system of names is rather complicated. Any one individual may be known by several different names and even by two

different clan names. Furthermore, since marriage between persons of the same name or "isibongo" is disfavoured, should two people with the same "isibongo" wish to marry, one or other spouse may take on the clan name of his or her mother and thus overcome the problem[156]. This makes the compilation of genealogies somewhat difficult.

5. Adoption practices: There are two interesting practices which complicate genealogical studies, and apparently still take place[21, 140].

Ngenisa: When a wife is barren, a younger sister may be brought to the husband to bear a child for him. This child is then given to the barren older sister and becomes her child. If questioned, both women will state that the child is that of the older sister.

Ukungena: When a man dies without offspring, a brother may impregnate the wife. The child is then said to be that of the dead man.

Although the two health assistants, who did the interviewing, were fully aware that we were concerned only with biological parentage and tried to make this clear at all times to the subjects interviewed, it is possible that on one or two occasions such inaccuracies could have been recorded.

III.2.1 PREVALENCE RATES IN THE HIGH PREVALENCE AND A CONTROL AREA

III.2.1 PREVALENCE RATES IN THE AFFECTED AREA AND A CONTROL AREA

Mseleni sections 1 to 10, Manaba sections 2 and 3 and Mbazwana sections 2 and 3 (Fig 3) were provisionally classified as the high prevalence area on the basis of the 1971 enumeration[57].

Sibaya sections 7 and 8 separated from Mseleni by Lake Sibaya sections 9 and 10 were thought to have a very low prevalence rate and were provisionally selected as a control area. A complete kraal-by-kraal census was carried out in the high prevalence area and in Sibaya sections 7 and 8. The interviewer classified each person listed in the census, as affected or unaffected. Dwarfed individuals were also noted. Any person with the typical symptoms or sign of MJD, i.e. pain and stiffness or walking disability, was classified as affected. Age specific prevalence rates for MJD for females in Mseleni are seen in Table I and for males in Table II. In Table III the age specific prevalence rates of MJD for females in Mseleni, Manaba, Mbazwana and Sibaya are compared, while in Table IV the same comparison is made for males.

Prevalence rates among females: A total of 2,825 females of all ages was recorded during the census. Of these 59,4% (1678) lived in Mseleni, 19,3% (546) in Manaba, 10,0% (281) in Mbazwana and 11,3% (320) in Sibaya. Generally, the prevalence rates increased steadily with age. In Mseleni, for the 1 - 9 year group, the prevalence was 0,5% while for the 60 - 69 year group it was 53,4%.

The highest prevalence rates were found in Mseleni section 3 and

TABLE I : AGE SPECIFIC PREVALENCE RATES OF MJD FOR FEMALES FOR EACH SECTION IN MSELENI (1973 ENUMERATION)

Age		Mseleni Section No.										
		1	2	3	4	5	6	7	8	9	10	Total
1	Total	58	68	20	28	58	9	19	41	37	52	390
to	Affected	0	1	0	0	1	0	0	0	0	0	2
9	% affected	0	1,5	0	0	1,7	0	0	0	0	0	0,5
10	Total	53	58	30	25	55	5	21		53	59	415
to	Affected	0	1	5	0	1	0	1	1	2	1	12
19	% affected	0	1,7	16,7	0	1,8	0	4,8	1,8	3,8	1,7	2,9
20	Total	29	40	13	21	31	7	15	19	24	43	242
to	Affected	1	6	3	1	5	0	1	3	1	2	22
29	% affected	3,4	15,0	23,1	4,5	16,1	0	6.7	15,8	4,2	4,6	9,1
30	Total	23	26	8	13	13	5	12	19	16	20	155
to	Affected	6	11	4	6	4	3	3	0	3	3	43
39	% affected	26,1	42,3	50,0	46,1	30,8	60,0	25,0	0	18,7	15,0	27,7
40	Total	35	41	18	14	32	4	8	33	28	29	242
to	Affected	12	24	14	7	18	0	4	9	10	8	106
49	% affected	34,3	58,5	77,8	50,0	56,2	0	50,0	27,3	35,7	27,5	43,8
50	Total	13	15	17	7	18	8	8	27	10	24	147
to	Affected	4	11	11	4	11	4	3	12	4	5	69
59	% affected	30,8	73,3	64,7	57,1	61,1	50,0	37,5	44,4	40,0	20,8	46,9
60	Total	14	8	3	5	3	2	1	7	3	11	57
to	Affected	7	6	2	0	2	2	1	4	2	5	31
69	% affected	50,0	75,0	66,7	0	66,6	100	100	57,1	66,7	45,4	53,4
70	Total	3	1	0	1	7	0	1	5	3	3	24
to	Affected	2	1	0	1	4	0	0	4	2	2	16
79	% affected	66,6	100	0	100	60,0	0	0	80,0	66,7	66,7	66,7
Age	Total	0	1	0	0	2	0	0	1	0	2	6
not	Affected	0	1	0	0	0	0	0	0	0	0	1
known	% affected	0	100	0	0	0	0	0	0	0	0	16,7
	Total	228	258	109	114	219	40	85	208	174	243	1678
Total:	Affected	32	62	39	19	46	9	13	33	24	26	303
	% affected	14,0	24,0	35,8	16,7	21,0	22,5	15,3	15,9	13,8	10,7	18,1

TABLE II : AGE SPECIFIC PREVALENCE RATES OF MJD MALES FOR EACH SECTION IN MSELENI (1973 ENUMERATION)

Age		Mseleni Section No										
		1	2	3	4	5	6	7	8	9	10	Total
1	Total	65	67	26	22	38	15	23	34	36	51	377
to	Affected	0	0	0	0	0	0	0	0	0	0	0
9	% affected	0	0	0	0	0	0	0	0	0	0	0
10	Total	49	36	9	10	29	6	17	43	35	39	273
to	Affected	0	0	0	1	1	0	0	2	0	1	5
19	% affected	0	0	0	10,0	3,5	0	0	0	0	2,6	1,8
20	Total	11	10	2	8	11	2	2	4	4	3	57
to	Affected	0	1	0	3	1	1	0	0	0	0	6
29	% affected	0	10,0	0	36,0	9,1	50,0	0	0	0	0	10,5
30	Total	10	10	2	5	8	3	2	3	3	6	52
to	Affected	2	1	0	0	2	2	0	0	0	1	8
39	% affected	20,0	10,0	0	0	25,0	66,6	0	0	0	16,7	15,4
40	Total	10	10	0	2	12	0	1	15	12	15	77
to	Affected	1	2	0	0	3	0	0	0	2	0	8
49	% affected	10,0	20,0	0	0	25,0	0	0	0	16,7	0	10,4
50	Total	4	5	2	4	6	0	0	11	11	10	53
to	Affected	1	0	0	0	1	0	0	1	2	2	7
59	% affected	25,0	0	0	0	16,6	0	0	9,1	18,2	20,0	13,2
60	Total	2	5	5	6	4	6	4	10	5	9	56
to	Affected	0	0	2	2	1	1	1	1	0	2	10
69	% affected	0	0	40,0	33,3	25,0	16,6	25,0	10,0	0	22,2	17,9
70	Total	5	2	1	2	0	0	2	1	0	1	14
or	Affected	0	0	0	0	0	0	0	1	0	0	1
older	% affected	0	0	0	0	0	0	0	100	0	0	7,1
Age	Total	0	2	0	0	0	0	0	1	1	2	6
not	Affected	0	0	0	0	0	0	0	0	0	0	0
known	% affected	0	0	0	0	0	0	0	0	0	0	0
Total	Total	156	147	47	59	108	32	51	122	107	136	965
	Affected	4	4	2	6	9	4	1	5	4	6	45
	% affected	2,6	3,7	4,3	10,2	8,3	12,5	1,9	4,1	3,7	4,4	4,7

TABLE III : COMPARISON OF AGE SPECIFIC PREVALENCE RATES OF MJD FOR FEMALES IN MSELENI, MANABA, MBAZWANA AND SIBAYA

		Mseleni	Manaba			Mbazwana			Lake Sibaya		
Age		Total	2	3	Total	2	3	Total	7	8	Total
1 - 9	Total	390	35	120	155	35	22	57	56	42	98
	Affected	2	0	0	0	0	0	0	0	1	0
	% affected	0,5	0	0	0	0	0	0	0	0	0
10-19	Total	415	48	54	102	44	32	76	41	22	63
	Affected	12	5	2	7	1	1	2	0	0	0
	% affected	2,9	10,4	3,7	6,7	2,3	3,1	2,6	0	0	0
20-29	Total	242	32	78	110	33	21	54	43	20	63
	Affected	22	10	11	21	4	0	4	1	0	1
	% affected	9,1	31,2	14,1	19,0	12,1	0	7,4	2,3	0	1,6
30-39	Total	155	12	31	43	9	11	20	18	14	32
	Affected	43	7	9	16	3	2	5	1	0	1
	% affected	27,7	58,3	29,0	37,2	33,3	18,1	25,0	5,5	0	3,1
40-49	Total	242	30	42	72	8	9	17	30	11	41
	Affected	106	20	12	32	2	1	3	3	2	5
	% affected	43,8	66,7	28,6	44,4	25,0	11,1	17,6	10,0	18,2	12,2
50-59	Total	147	14	28	42	21	7	28	13	2	15
	Affected	69	11	8	19	10	2	12	5	1	6
	% affected	46,9	78,6	28,6	45,2	47,6	25,8	42,9	38,5	5,0	40,0
60-69	Total	57	11	9	20	16	6	22	2	3	5
	Affected	31	9	4	13	10	3	13	2	0	2
	% affected	53,4	81,8	44,4	65,0	62,5	50,0	59,1	100	0	40,0
70 +	Total	24	0	0	0	3	7	1	1	1	2
	Affected	16	0	0	0	2	4	0	0	1	1
	% affected	66,7	0	0	0	66,7	57,1	0	0	100	50,0
Age not stated	Total	6	0	2	2	0	0	0	1	0	1
	Affected	1	0	0	0	0	0	0	0	0	0
	% affected	16,7	0	0	0	0	0	0	0	0	0
Total	Total	1678	182	364	546	169	112	281	205	115	320
	Affected	302	62	46	108	32	11	43	12	4	16
	% affected	18,0	34,1	12,6	19,8	18,9	9,8	15,3	5,9	3,5	5,0

TABLE IV : COMPARISON OF AGE SPECIFIC PREVALENCE RATES OF MJD FOR MALES BETWEEN THE FOUR AREAS

Age		Mseleni	Manaba			Mbazwana			Lake Sibaya		
		Total	2	3	Total	2	3	Total	7	8	Total
1	Total	377	37	115	152	32	19	51	50	33	83
to	Affected	0	1	0	1	0	0	0	0	0	0
9	% affected	0	2,7	0	0,7	0	0	0	0	0	0
10	Total	273	29	56	85	40	24	64	23	14	37
to	Affected	5	3	0	3	0	0	0	0	0	0
19	% affected	1,8	10,3	0	3,5	0	0	0	0	0	0
20	Total	57	7	15	22	4	5	9	9	5	14
to	Affected	6	0	0	0	0	0	0	0	0	0
29	% affected	10,5	0	0	0	0	0	0	0	0	0
30	Total	52	6	23	29	1	4	5	8	3	11
to	Affected	8	1	2	3	0	0	0	0	0	0
39	% affected	15,4	16,7	8,7	10,3	0	0	0	0	0	0
40	Total	77	10	13	23	7	5	12	5	8	13
to	Affected	8	0	1	1	0	0	0	0	0	0
49	% affected	10,4	0	7,7	4,3	0	0	0	0	0	0
50	Total	53	7	12	19	7	1	8	7	7	14
to	Affected	7	1	4	5	5	1	6	0	1	1
59	% affected	13,2	14,3	33,3	26,3	71,4	100	75,0	0	14,3	7,1
60	Total	56	2	14	16	9	4	13	3	1	4
to	Affected	10	0	0	0	2	1	3	0	0	0
69	% affected	17,9	0	0	0	22,2	25,0	23,1	0	0	0
70	Total	14	0	2	2	4	0	4	2	0	2
to	Affected	1	0	1	1	3	0	3	1	0	1
79	% affected	7,1	0	50,0	50,0	75,0	0	75,0	50,0	0	50,0

/Continued on next page

Table IV continued

Age		Mseleni	Manaba			Mbazwana			Lake Sibaya		
		Total	2	3	Total	2	3	Total	7	8	Total
Age not stated	Total	6	0	1	1	1	3	4	1	0	1
	Affected	0	0	0	0	0	1	1	0	0	0
	% affected	0	0	0	0	0	33,3	25,0	0	0	0
Total	Total	965	98	251	349	105	65	170	108	71	179
	Affected	45	6	8	14	10	3	13	1	1	2
	% affected	4,7	6,1	3,2	4,0	9,5	4,6	7,6	0,9	1,4	1,1

Manaba section 2 while the lowest rates were found in Sibaya. The prevalence rate for all women in Mseleni section 3 was 35,8%, for Manaba section 2 was 34,1% and for Sibaya sections 7 and 8, 5,9% and 3,5%, respectively. When the females are grouped into children (under 20 years and adults (20 years and over), the prevalence rates for the 2 groups in each area may be seen in Table

TABLE V : PREVALENCE RATES AMONG FEMALES FOR ADULTS AND CHILDREN IN THE FOUR SECTIONS

		Mseleni	Manaba			Mbazwana			Lake Sibaya		
Age 1-19		To-tal	2	3	To-tal	2	3	To-tal	7	8	To-tal
	Total	805	83	174	257	79	54	133	97	64	161
	Aff.	14	5	2	7	1	1	2	0	0	0
	% aff.	1,7	6,0	1,2	2,7	1,3	1,9	1,5	0	0	0
20-70											
	Total	867	99	188	287	90	58	148	107	51	158
	Aff.	287	57	44	101	31	10	41	12	4	13
	% aff.	33,1	57,6	23,4	35,2	34,4	17,2	27,7	12,4	7,8	8,2

Prevalence rates for men: A total of 1663 males of all ages were recorded during this census. The breakdown per area was Mseleni 58,0% (965). Manaba 21,0% (349), Mbazwana 10,2% (170) and Sibaya 10,8% (179). The prevalence rates are significantly lower than those for the females.

The highest overall rates are those in Mseleni sections 6 (12,5%) and 4 (10,2%) in Mbazwana section 2 (9,5%). When the males are grouped into children (under 20 years) and adults (20 years or more) the preva-

lence rates are as seen in Table

TABLE VI : PREVALENCE RATES AMONG MALES FOR ADULTS AND CHILDREN IN THE FOUR SECTIONS

		Mseleni	Manaba			Mbazwana			Lake Sibaya		
Age 1-19		To-tal	2	3	To-tal	2	3	To-tal	7	8	To-tal
	Total	650	66	171	237	72	43	115	73	47	120
	Aff.	5	4	0	4	0	0	0	0	0	0
	% aff.	0,8	6,1	1,0	1,7	0	0	0	0	0	0
Age 1-19											
	Total	315	32	79	111	32	19	51	34	24	58
	Aff.	40	2	8	10	10	2	12	1	1	2
	% aff.	12,7	6,3	10,0	9,0	31,3	10,5	23,5	2,9	4,2	3,5

The prevalence rates recorded among both males and females are consistently lower than in the previous 1971 enumeration. The reason for this is not readily apparent. The population enumerated would not have altered greatly in two years. The health assistant who conducted the first enumeration trained the second health assistant who helped him carry out the second census and the census methods should thus be similar.

A comparison is being made between the 1971 and 1973 survey and a check will be made where results differ, but this is not as yet complete.

The accuracy of the prevalence rates will be discussed in section II.2.3 in relation to the radiological findings. It is possible that people who were reluctant to be examined or to give blood, knowing of the survey work decided to be prudent during the second enumeration, and

denied any disability. In fact this seems the most likely explanation.

High prevalence area compared to control area

The comparative prevalence rates for MJD of 32,9% and 8,2% for females in the high prevalence and Sibaya areas respectively and of 15% and 3,5% for males in these areas at first created the impression that Sibaya had too high a prevalence rate to be a control area.

However, the obvious difference in prevalence rates suggested that a further investigation of Sibaya cases should be carried out. This is reported in Section III.2.6.

III.2.2 A STUDY OF THE CLINICAL FEATURES OF MSELENI JOINT DISEASE

III.2.2: A SURVEY OF AFFECTED PERSONS

All people listed during the census as suffering from MJD were interviewed by one of the field-workers, unless they were out of the area during the survey period. During these interviews a Symptom Form was completed for each affected person. Altogether 321 forms were available for inclusion in this study. These consisted of forms from 52 males and 269 females. Since the enumeration showed 74 affected males and 466 affected females, the proportion interviewed was some 70% of males and 58% for females.

The age distribution of the sample under study appears to be representative of the age distribution of affected people obtained in the enumeration, but a greater proportion of affected men than affected women were interviewed. The age distribution of the sample can be seen in Table VII.

Disability caused by the joint disease was categorised under 5 headings ranging from joint pain to being bedridden. The degree of disability of the subjects at the time of interview has been tabulated against the age and sex in Table VII.

Degree of disability

(a) Sex differences: For both males and females the highest proportion of cases, approximately 48% in both sexes, are in category 3. That is they use one or two sticks as a crutch in order to walk. The next highest group is that in category 2, 30% for men and 29% for females. These people have walking difficulty

TABLE VII : THE DEGREE OF DISABILITY TABULATED AGAINST THE AGES AND SEX OF THE SUBJECTS (NUMBER AND PERCENTAGE OF SUBJECT IN EACH CATEGORY)

Age group	Males							Females							Total in Age group	
	Degree of disability							Degree of disability								
	1	2	3	4	5	6	Total	1	2	3	4	5	6	Total		
0-9	0	0	0	0	0	0	0	1 2,8	1 1,3	1 0,8	0	0	0	3 1,1	3	0,9
10-19	1 11,1	2 12,5	0	1 100,0	0	0	4 7,7	3 8,3	3 3,9	0	1 5,9	0	0	7 2.6	11	3,4
20-29	1 11,1	1 6,3	1 4,2	0	0	1 50,0	4 7,7	5 13,9	9 11,7	5 3,8	1 5,9	0	0	20 7,4	24	7,5
30-39	1 11,1	5 31,3	0	0	0	0	6 11,5	7 19,4	14 18,2	9 6,9	1 5,9	0	0	31 11,5	37 37	11,5 11,5
40-49	0	3 18,8	3 12,5	0	0	0	6 11,5	7 19,4	27 35,1	44 33,8			3 33,3	81 30,1	87 87	27,1 27,1
50-59	2 22,2	2 12,5	7 29,2	0	0	1 50,0	12 23,1	8 22,2	15 19,5	40 30,8	6 35,3	0	4 44,4	73 27,1	85	26,5
60-69	4 44,4	3 18,8	8 33,3	0	0	0	15 28,8	4 11,1	7 9,1	21 16,2	5 29,4	0	1 11,1	38 14,1	53	16,5
70-79	0	0	5 20,8	0	0	0	5 9,6	1 2,8	1 1,3	10 7,7	3 17,6	0	1 11,1	16 5,9	21	6,5
Total:	9	16	24	1	0	2	52	36	77	130	17	0	9	269	321	100

KEY: 1 = Pain in joints
2 = Walks with difficulty
3 = Needs stick in order to walk
4 = Crawls on hands and knees
5 = Bedridden
6 = Degree of disability not recorded

due to pain, stiffness and rapid fatigue. There were no people in category 5 (bedridden) and only 1 man in category 4 (able only to crawl) Category 1, joint pain only, included 17% of men and 13% of women.

It can be seen that the percentage of persons in each category does not vary greatly between the sexes.

(b) Effect of age: In the 0 - 9 group, there were no boys included and only 3 girls. Of these, one was classed in category 3, requiring a stick in order to walk.

It may be seen that from the 10 to 19 year group upward, persons are classed in category 4, i.e. crawl on hands and knees. It is probable that the 2 in the 10 to 19 year group are crippled by polio rather than MJD as they do not complain of joint pain but only inability to walk. At least one case of crippling due to polio was stated to be a joint case by the family.

The cases were categorised by the field assistants on a basis of symptoms and they would not necessarily distinguish between crippling due to MJD or another cause. Furthermore, it can be seen that although disability increases with age, even above 50 years only a few patients progress to stage 4.

Onset of symptoms

Age at onset: Each person was asked to estimate the age at which symptoms of MJD began. The distribution of the approximate age of onset for the subjects may be seen in Fig. 10. Among the male subjects the peak age

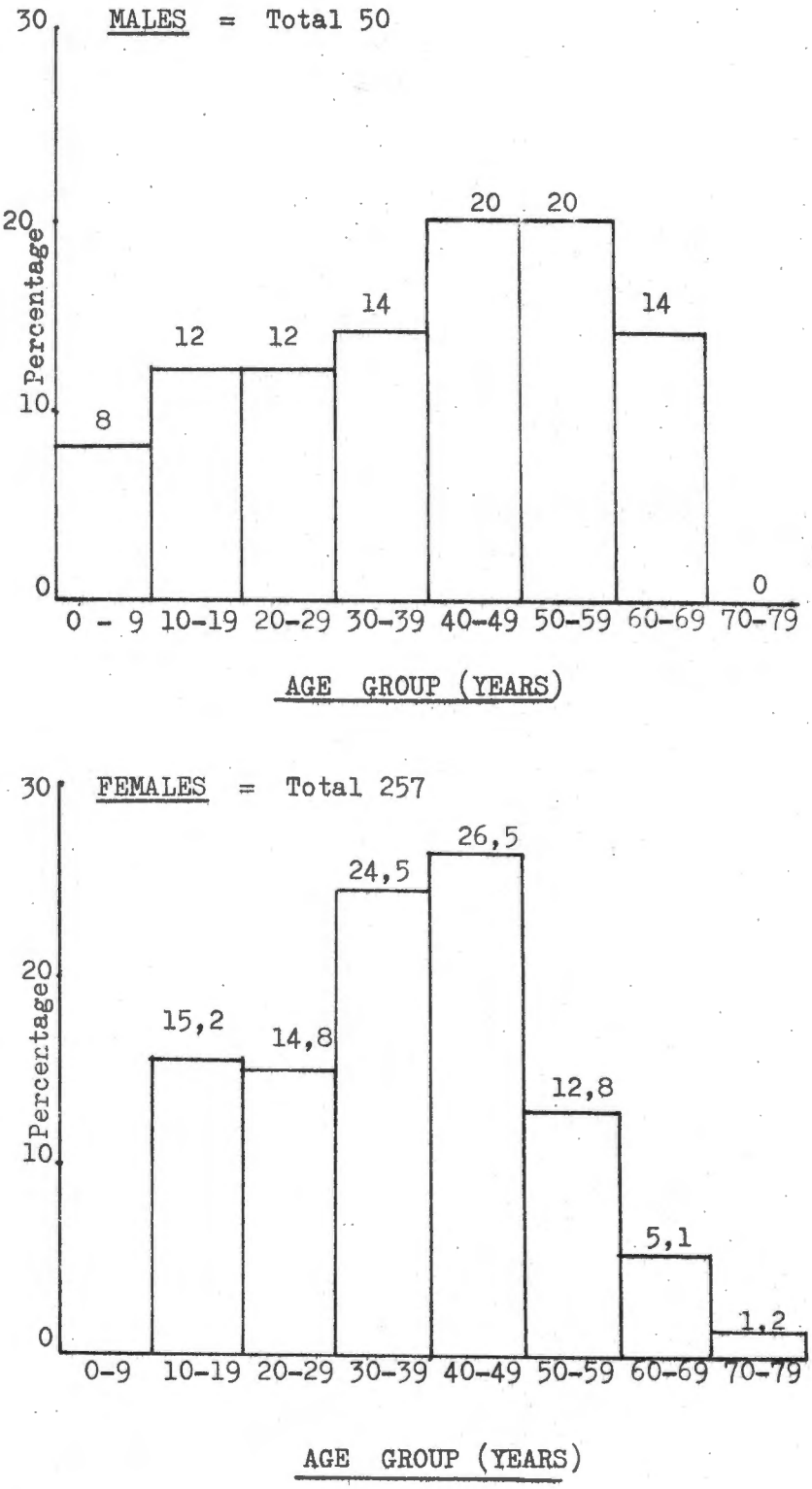


Fig. 10 : Age at onset of symptoms for males (top histogram) and females (lower histogram)

period for onset of symptoms was between 40 and 60 years during which period approximately 38% developed symptoms. For the females the peak period of onset was between 30 and 50 years, during which time some 48% of the females developed symptoms.

No age of onset was recorded for 1 man and 12 women. However, the following two questions regarding age group at onset, and relationship to reproduction were answered by the 12. Two were grouped into the "pre-school" age period, "2 into the post school but without children" group, 5 into the "middleaged" group and 3 developed symptoms when elderly.

Age period at onset

Since age and time concepts among this population are of doubtful accuracy, each person was later asked at which age period the symptoms began. The age group at onset of symptoms is tabulated for males, females, and the combined sample in TableVIII. The relationship of onset of symptoms to the reproductive period for women may be seen in Table IX.

TABLE VIII: AGE PERIOD AT ONSET OF SYMPTOMS OF JOINT DISEASE

Age period at onset	Males*		Females		Total	
Pre-school age	1	2,0%	4	1,5%	5	1,6%
School-going	11	21,6%	30	11,2%	41	12,8%
Post-school without children	4	7,8%	23	8,6%	27	8,4%
Middle-aged	29	56,9%	187	69,5%	216	67,5%
Elderly	6	11,8%	25	9,3%	31	9,7%

* No age group or age of onset was recorded for 1 man.

TABLE IX : RELATIONSHIP OF ONSET OF JOINT DISEASE SYMPTOMS TO REPRODUCTIVE PERIOD IN FEMALES

Period of onset	No. of females	Percentage
Prepubertal	19	7,1
Pubertal	28	
Adult but nulliparous	11	10,4
After first baby was born	21	7,8
After two or more babies were born	190	70,6
Total:	269	100%

Relationship of onset of disease to systemic symptoms

The subjects were asked whether the joint pains first began during an acute illness, or whether the pain developed gradually. This information is tabulated in Table X.

TABLE X : RELATIONSHIP OF ONSET OF DISEASE TO SYSTEMIC SYMPTOMS

Appearance of symptoms	Male		Female		Total	
Associated with an acute illness	2	3,8%	3	1,1%	5	1,6%
Gradual onset	50	96,1%	264	98,9%	314	98,4%
Total:	52		267*		319	

* No answer recorded for 2 women.

The number who associated the onset of MJD symptoms with an acute illness were asked to list the systemic symptoms.

Two males and 3 females stated that the onset of joint symptoms was related to an acute illness. One man and 2 women stated that the symptoms began when they had chest pain as a result of tuberculosis. Their ages were 70, 60 and 50 years and the onset of symptoms was between 3 and 6 years previously. Possibly their pain related to senile osteoporosis rather than MJD. A 50 year old woman with pain of 6 years duration dated it to a fall. The remaining 2 people related their onset of pain to a time when they had "bladder pain" and "headache and boils", respectively.

Almost 96% of the women and 99% of the men stated that the pain developed gradually and it seems obvious that there is no acute inflammatory episode precipitating the joint disease.

Distribution of affected joints

The patients were asked which joints were painful at the present time and in which joints the pain was first felt. This data is tabulated in Tables XI and XII.

TABLE XI : NUMBER OF PATIENTS WITH PAIN IN EACH JOINT

AT THE PRESENT TIME

Joints	Males	% of male group	Joints	Females	% of female group
Hips	43	81,1	Knees	228	85,1
Knees	36	67,9	Ankles	225	84,0
Ankles	32	60,4	Hips	217	81,0
Shoulder	1	1,9	Hands/ fingers	7	2,6
Hands/ fingers	1	1,9	Back	2	0,7
			Feet	2	0,4
			Shoulders	1	0,4

TABLE XII : JOINTS IN WHICH PAIN WAS FELT FIRST, SECOND, THIRD

Males	Affected joint	First	Second	Third
	Ankles	29 (54,7)	0 (0,0)	1 (1,9)
	Hip	13 (24,5)	10 (18,7)	18 (34,0)
	Knees	8 (15,1)	25 (47,2)	0 (0,0)
	Shoulder	0 (0,0)	1 (1,9)	0 (0,0)
	Fingers	0 (0,0)	0 (0,0)	1 (1,90
Females				
	Ankles	188 (70,1)	6 (2,2)	1 (9,0)
	Hips	44 (16,4)	23 (8,6)	145 (54,1)
	Knees	24 (9,0)	193 (72,0)	1 (0,4)
	Feet	1 (0,4)		

It is interesting to note that while the same percentage of men and women complain of hip pains, there is a significantly higher percentage of women complaining of pain in the knees and ankles. The large joints of the upper limbs are not responsible for much of the symptomatology, though the hands and fingers are painful in a small percentage of cases.

Effect of MJD on daily life

The patients were asked to describe how their joint disease affected daily life. Their answers are tabulated in Table XIII.

TABLE XIII : EFFECT OF MJD ON DAILY LIFE

Effect on daily life	No. of patients	Percentage of total patients
None	45	14,0
Can work but is in pain	70	21,8
Cannot carry water	135	42,1
Cannot hoe	63	19,6
Cannot work at all in the fields	43	13,4

Affected relatives

In view of a suggestion that the high prevalence of disease could have been due to an epidemic of some infective disorder of the joints such as brucellosis, the patients were asked whether any other family members developed symptoms of MJD at the same time as themselves. Only one answered in the affirmative. She said that her mother developed joint pains when her joint pains began. They were also asked whether

there were any dwarfs in their family. Twenty-two were related to dwarfs. Sixteen had a brother who was dwarfed, three, a sister while in six cases the dwarf was a son or daughter, one a nephew, one a grandchild while six of these people had two dwarfed relatives.

The final question was whether any relatives not living in the same kraal as the subject suffered from MJD. The number of patients with such relatives can be seen in Table XIV.

TABLE XIV : PATIENTS WITH AFFECTED RELATIVES LIVING IN ANOTHER KRAAL

Relative	No. of patients	Percentage of total patients
Mother	17	5,3
Father	44	1,2
Sister	52	16,4
Brother	12	3,7
Aunt	1	0,3
None	236	73,5

In contrast, 46 subjects lived with at least one other affected person in the kraal, In 29 cases, there were two affected people in the kraal, in 12 cases, 3 in 3 cases, 4, and in 2 cases 5 affected people in the kraal.

This information was then checked against the information from the family history forms in constructing genealogical charts.

EXAMINATION OF AFFECTED SUBJECTS

This description is based on the examination of affected and adult members of the families investigated for the genealogical studies, as well as other affected members of the population.

The information obtained from the symptom forms, which was presented in the last section was confirmed by personal discussion with the patients.

The majority of women related the onset of pain to the time following the birth of their children. Pain was often present at rest and aggravated by walking. Aching was commonly noted at night. Although the odd patient complained of a cough, diarrhoea or haematuria, the majority denied any symptoms other than pain and stiffness of the joints.

The older affected patients could be recognised by the distinctive gait and posture. The characteristic posture is that of the women illustrated in Fig. 6. The patient usually leans on a stick. The back is flexed forward at the hip joint, and there is a marked lumbar lordosis.

The gait is slow, stiff and shuffling in the older patients but the younger patients tend to waddle. Many patients have severe degrees of genu valgum. Some of the older women have pronounced Heberden's nodes.

A few of the older affected children can be recognised by their slightly enlarged knee joints and a somewhat waddling gait but many of the children with severe radiological changes cannot be differentiated from their unaffected peers.

Affected people may be short or tall. A number of dwarfed adults were noted. They are discussed separately in section II.2.5.

The heights of 71 of the men and 87 of the women who were examined radiologically as part of the random sample of men and women from the high prevalence area (see Section III.2.3) were recorded. They were classed into either an affected or unaffected group based on the radiological phenotype, and the heights of the two groups were compared.

TABLE XV : COMPARISON OF HEIGHTS BETWEEN AFFECTED AND UNAFFECTED PEOPLE BASED ON RADIOLOGICAL PHENOTYPE

Males	No.	Mean	Range	S.D.
Normal	64	165,0	151,3 - 181,3	6,5
Affected	7	165,8	148,8 - 176,3	8,3
		No significant difference (P> 0,5)		
Females	No	Mean	Range	S.D.
Normal	56	155,0	141,3 - 165,0	5,8
Affected	31	150,5	131,3 - 162,5	6,3
The difference is significant (F<0,01)				

There was no significant difference between the mean heights of affected and unaffected men; However the sample of affected men was small and it is possible that a larger sample might reveal a difference.

A significant difference was found between the heights of affected and unaffected women.

The only consistent positive findings on examination related to the skeletal system. Occasional patients were found to have bronchitis, tonsillitis, otitis media and other similar disorders but on the whole despite the low standard of nutrition prevalent in the area, the general health was good.

In the skeletal system the symptomatology and findings on examination were those of a non-acute arthrosis. Contractures and decreased ranges of movement were noted particularly in the hip joints but abnormalities were commonly found in all the major joints and the small joints of the hand. The older patients were most severely affected.

Many of the younger children including those with severe radiological joint abnormalities appeared completely normal on examination and showed a full range of movements in all joints.

No evidence of acute arthritis was found. Crepitus was a common finding in the knee and ankle joints.

CONCLUSIONS FROM SECTION III.2.2

1. The degree of crippling caused by the disease increases (as would be expected) with age, but in the majority of cases, as it was noted that the resultant disability is not more than the need to use a form of support or crutch in order to walk.
2. The peak age of onset of symptoms was in early middle age for females and later middle age for males. However, symptoms could begin at any stage.
3. The onset of pain was gradual and unrelated to systemic illness or acute inflammatory disease of the joints. There was no evidence to suggest that an epidemic of infective joint disease was responsible for the disorder.
4. Males complained most frequently of pain in the hips, then knees and then hips for females the sites were knees, ankles and the hips.
5. Only 14% stated that the joint disease did not affect their daily life; while the remainder complained of inability to perform one or more of their expected tasks without pain.
6. Severely affected people could be identified by the characteristic posture and stance. Younger or asymptomatic affected people could often not be identified.
7. A significantly lower height was found in affected females when compared with normal females.
8. The disorder in the older patients appeared to be chronic degenerative multiple joint disease.
9. No consistent abnormality was present in any but the skeletal system.

III.2.3 A STUDY OF THE RADIOLOGICAL FINDINGS OF MSELENI JOINT DISEASE

III.2.3 A STUDY OF THE RADIOLOGICAL FEATURES OF MSELENI JOINT DISEASE

Objectives: The purpose of this study was to define the type of radiological abnormalities of MJD for various groups and the various joints and to derive frequency rates for the occurrence of these abnormalities.

Methods: The description of the types of abnormality is based on a study of some 300 affected adults and children. These were drawn in part from a random sample of the population of the high prevalence and a control area, and in part from those people studied in the genealogical investigations described in section III.2.4.

The prevalence figures for the various abnormalities are however, based only on the random sample of 242 adults from the high prevalence area and 82 adults from the control area. They are compared with a random sample obtained from Bantu patients examined at the H.F. Verwoerd Hospital in Pretoria.

The joints which were examined were the hips, knees, ankles, feet, hands and thoraco-lumbar spine in most cases. Elbows and shoulders were examined in about one quarter of the people. In the case of the people from the control area, only the hips, hands and feet were examined.

Results: Five groups of abnormalities were found on examination of affected people.

1. Abnormalities of the epiphyses and occasionally of the metaphyses of the diarthrodial joints.
2. Evidence of degenerative joint changes in the diarthrodial joints.

3. Deformities of the carpal and tarsal bones.

4. Anomalies of certain of the long bones and of the metacarpals and metatarsals.

5. Protrusio acetabuli.

For the purpose of the studies described in this thesis, isolated protrusio acetabuli was considered as a separate entity. The other four categories were graded in general into four degrees of severity. The grading was as follows:-

- = Unaffected.

\+ = Mild, but definite abnormality.

++ = Moderately severe abnormality.

+++ = Marked degree of abnormality.

In grading the osteoarthritic or degenerative joint changes, in an attempt to discount minimal or "wear and tear" abnormalities in the adult subjects, a slight modification of Kellgren and Lawrence's categories 90b was adopted.

They have graded osteoarthrosis into 4 categories. Grade 1 includes minimal or doubtful radiological changes.

Grade 2 includes cases with minimal but definite osteoarthrosis, such as those where osteophytes are present but the joint space is not obviously affected.

Grade 3 includes cases with a moderate degree of joint space narrowing and subchondral bone sclerosis, while

Grade 4 is severe osteoarthrosis.

For the purpose of these studies, cases with Grade 1 changes have been considered as unaffected by MJD. Where only a mild osteophytosis is present, this is regarded as a negative finding. Category + includes these cases where an obvious osteophytosis is accompanied by some joint space narrowing. Category ++ is equivalent to a Grade 3 abnormality and category +++ to a Grade 4.

In general, the radiological findings vary with age group. The typical findings are discussed for the child, the young adult and the elderly person, and then the range of findings for each joint is also described.

Radiology of the joints in the child with MJD.

The typical appearance of the abnormal joints in the severely affected child is seen in Figs. 11 to 17. In general, the epiphyses of the joints are small, flattened and irregular in form and density.

The articular surfaces in the knees and ankles are distorted and irregular. The carpal and tarsal bones are small and abnormal in shape while flattening and irregularity is also seen in the metatarsal heads. Fig. 16 the spine of an 8 year old boy, illustrates early anterior wedging with end plate irregularity while that in Fig. 15, the spine of an 11 year old, already clearly shows posterior humping.

Marked radiological abnormalities have been noted in children as young as 6 years of age, most of whom were asymptomatic. No abnormally formed epiphyses have been seen in children younger than about 6 years. As ages are only estimates, and the stunting effect of MJD in severe cases means that size is not a reliable indicator, it is almost impossi-

RADIOGRAPHS OF THE JOINTS OF CHILDREN WITH MSELENI JOINT DISEASE

Figure 11 : Hips joints of a 10 year old girl showing bilateral epiphyseal dysplasia.

Figure 12 : Feet of a 10 year old boy showing dysplasia of the metatarsal heads and irregularity of the borders of the talus and navicular bones.

Figure 13 : Knees of a 10 year old boy showing irregularity of both the femoral and tibial articular surfaces.

Figure 14 : Ankle of a 10 year old girl showing irregularity of both articular surfaces.

Figure 15 : Thoraco-lumbar spine of an 11 year old boy showing posterior humping of the vertebral bodies.

Figure 16 : Thoraco-lumbar spine of an 8 year old boy showing anterior wedging of the vertebral bodies.

Figure 17 : Hand of an 11 year old boy showing multiple abnormalities.

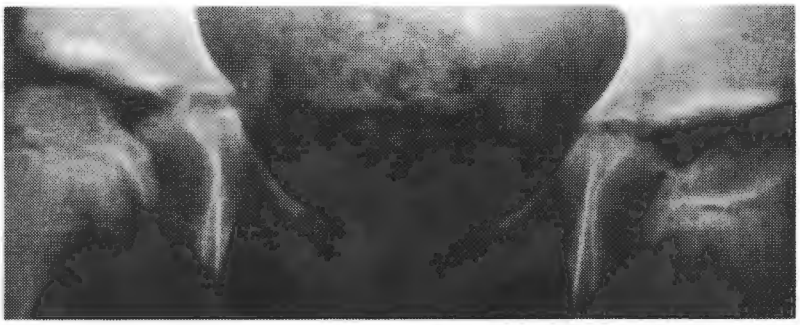
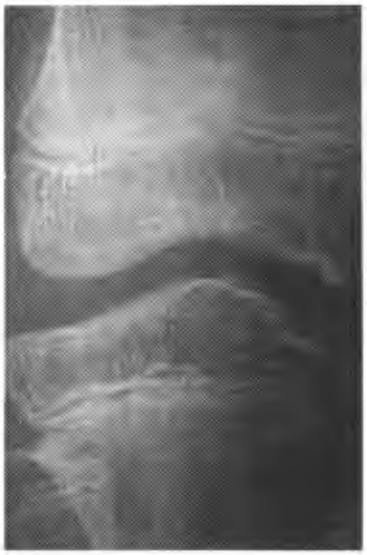


Fig. 11:



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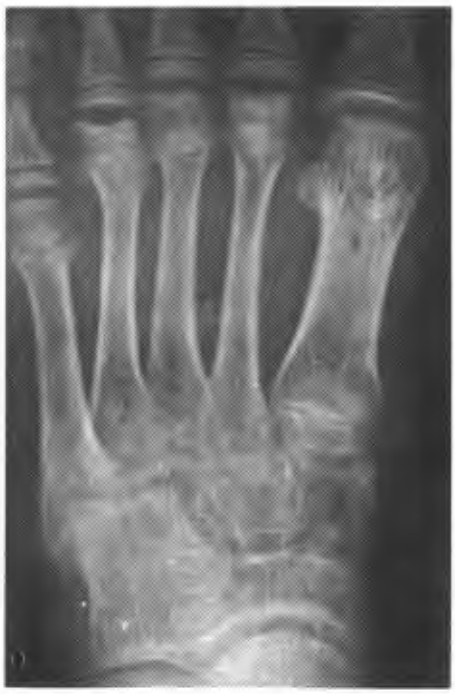
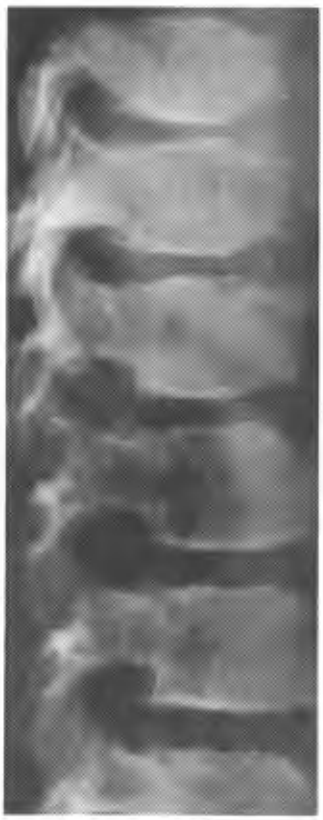


Fig. 12:

Fig. 14:

Fig. 15:



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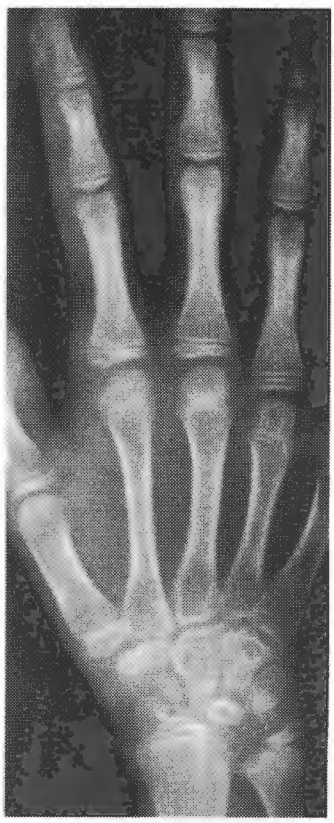

Fig. 17:

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ble to tell at present whether the appearance of epiphyseal ossification centres is accelerated or retarded.

In the affected children, as in the adults, not all the joints are involved and the findings in the affected joints of a single individual may range from a mild to a severe abnormality.

Since young people in their late teens may be seen with only mildly irregular and flattened epiphyses which may well have appeared normal at an early age, follow-up studies are required to see whether abnormalities develop in children apparently normal at 8 or 9 years of age.

The radiological appearance in the young adult:

The joint abnormalities in this group range from epiphyseal dysplasia with early degenerative joint changes to severe osteoarthrosis with total joint disruption.

Anomalies of metacarpal length and of the length of radius and ulna are most apparent in this age group.

These findings are illustrated from Fig. 18 onward with examples of the range of abnormalities in each joint grouped together.

Radiology of the joints of the elderly person with Mseleni Joint Disease:

The characteristic radiological appearance of the joints affected in the elderly person with MJD is that of a severe degree of osteoarthrosis. This is usually a multiplex osteoarthrosis affecting several different joints.

Different joints are involved and to a different degree in various individuals. This can be clearly seen later in the family studies in section III.2.4. Occasionally, an underlying deformity or predisposing factor such as obvious epiphyseal dysplasia may be evident, but in most cases the degenerative changes are so severe that any underlying dysplasia is masked.

These abnormalities may be seen in the figures illustrating the range of abnormalities for each joint.

The radiological appearance of the hip joint in Mseleni Hip Disease

The earliest detectable abnormality in the hip joint is a widened joint space due to an irregular flattening of the femoral head (See Fig. 18). This may be associated with a cystic appearance. The femoral head may be micro-epiphyseal. Later the femoral head becomes somewhat mushroomed and marginal osteophytes develop.

Mild abnormality: This consists of slightly irregular and flattening of the femoral head (Fig. 18).

Moderate abnormality: This consists of a greater degree of femoral head irregularity often with a cystic appearance and flattening. A degree of osteoarthrosis may be superimposed (Fig. 19).

Severe abnormality: The severe degree of abnormality of the femoral head may be either a greatly deformed, cystic and irregular epiphysis or a gross osteoarthrosis with large osteophytes and total loss of cartilage space (Fig. 20).

RADIOGRAPHS TO ILLUSTRATE TYPICAL FINDING IN:

HIPS

Figure 18 : Dysplasia of the femoral head and widened joint space. (Grade +)

Figure 19 : Mushrooming of the femoral head. (Grade +++).

Figure 20 : Dysplasia with early osteoarthrosis. (Grade +++).

Figure 21 : Marked osteoarthrosis with protrusio acetabuli (Grade +++).

KNEES

Figure 22 : Irregularity of tibial and femoral articular surfaces. Slightly flattened fibula. (Grade +++).

Figure 23 : Osteoarthrosis. (Grade ++).

ANKLES

Figure 24 : Osteochondritis of the talus. (Grade +).

Figure 25 : Dysplasia of both talar and tibial articular surfaces. (Grade ++).

Figure 26 : Slant sign - obliquity of ankle articular surface (Grade +++).

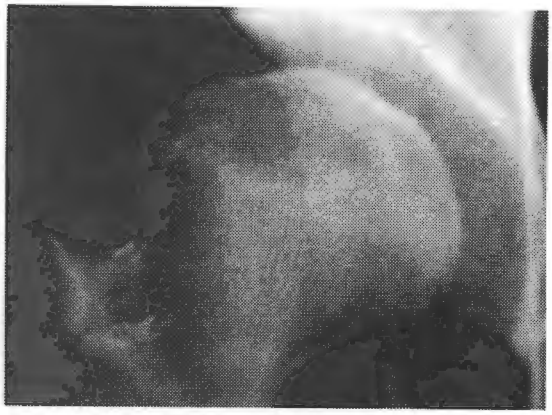
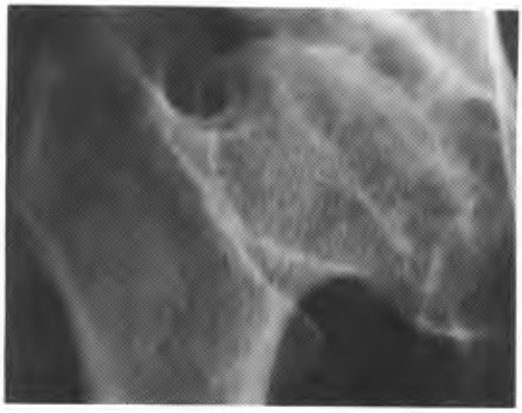


Fig. 18:



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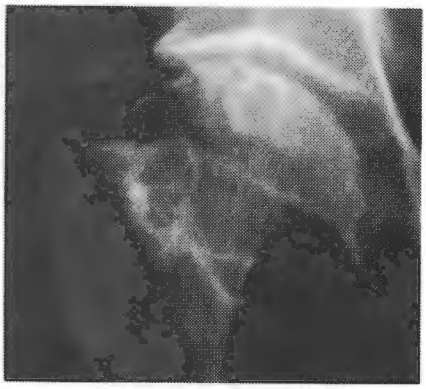
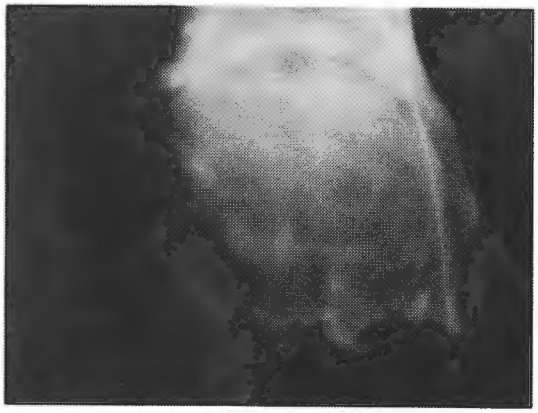


Fig. 20



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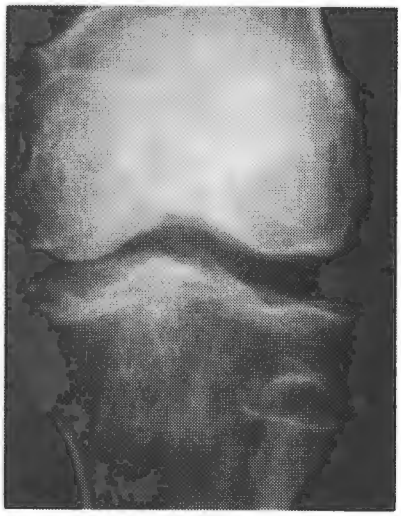

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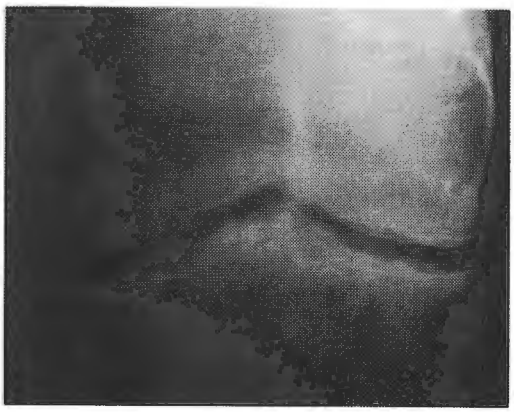

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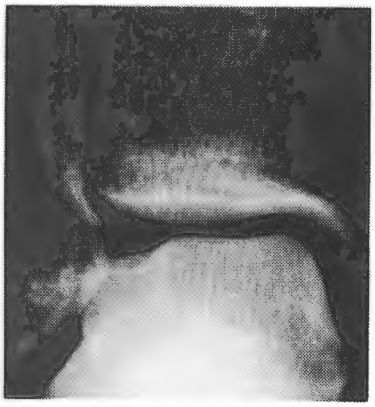
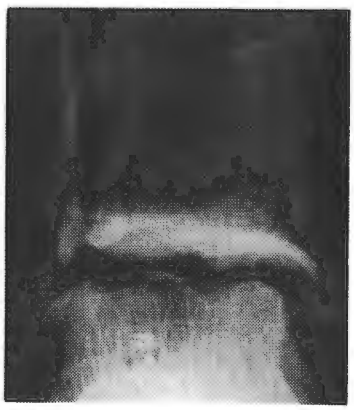


Fig. 24:



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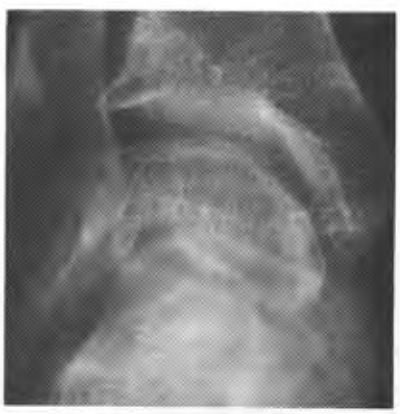

Fig. 26:

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TYPICAL FINDINGS IN THE ANKLES

Figure 27 : Osteoarthrosis of the ankle joint. (Grade ++).

FOOT

Figure 28 : Short first metatarsal, dysplasia of metatarsal heads and irregularity and flattening of talus and navicular bone. (Grade +++).

Figure 29 : Dysplasia of the metatarsal heads. (Grade +).

Figure 30 : Osteoarthrosis of several joints. (Grade ++).

Figure 31 : Short first metatarsal (Grade +++).

SHOULDERS

Figure 32 : Osteoarthrosis of shoulder. (Grade ++).

ELBOWS

Figure 33 : Osteoarthrosis of elbow. (Grade ++).

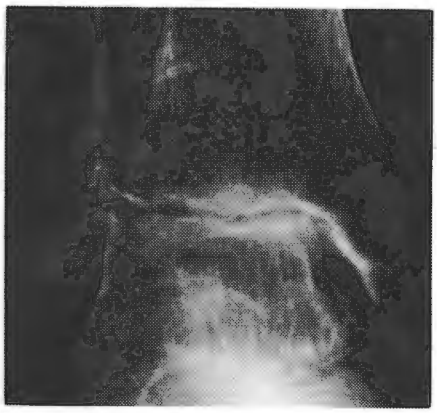
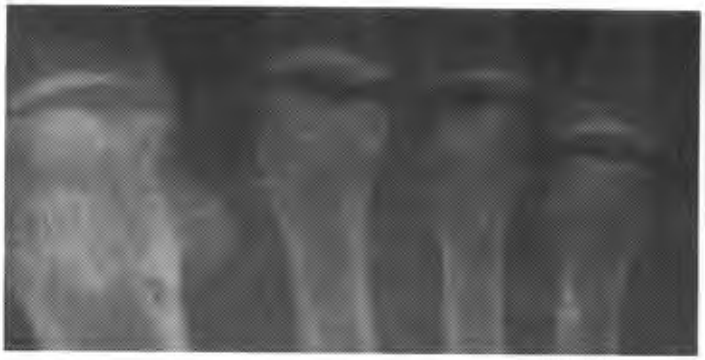


Fig. 27:



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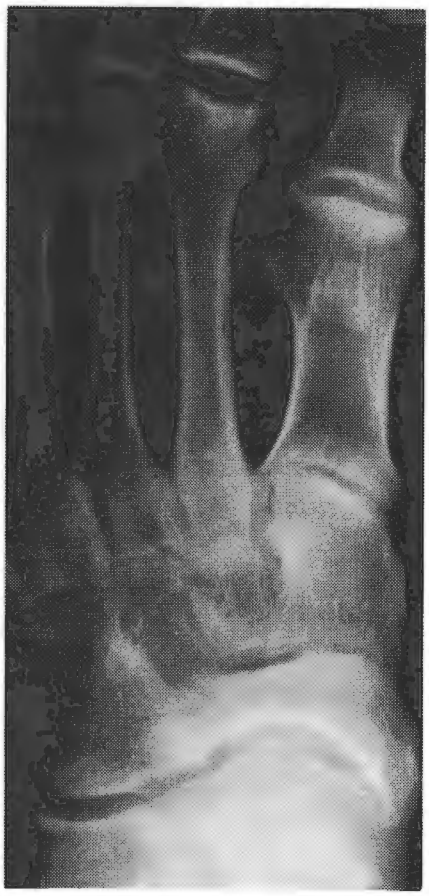
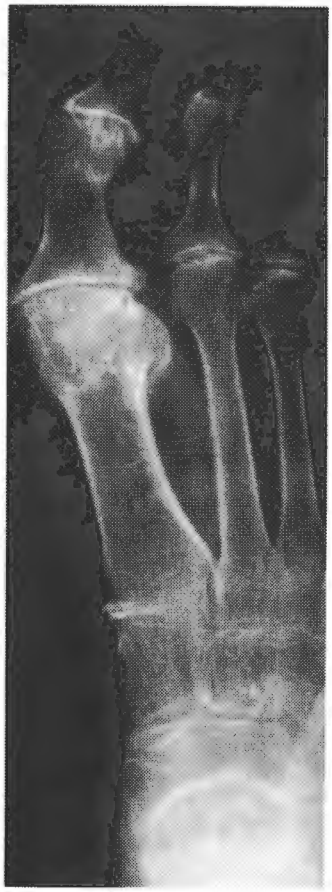


Fig. 28:



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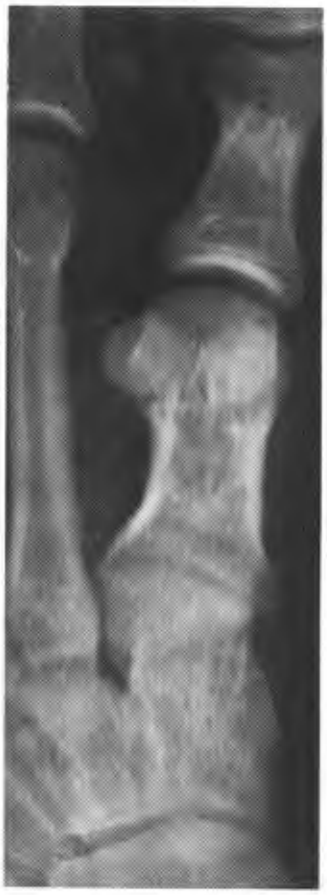

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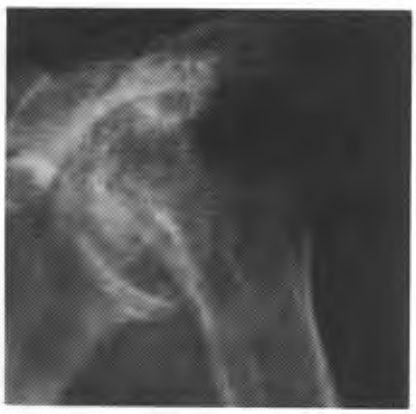

Fig. 32:

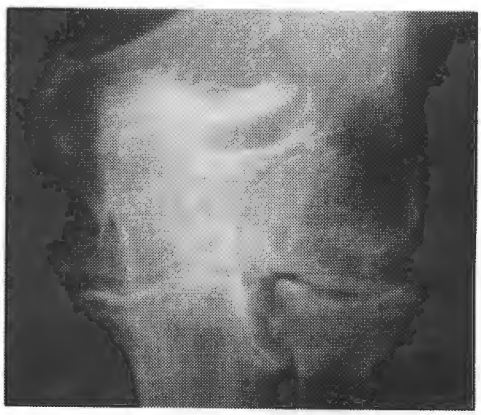

Fig. 33:

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TYPICAL FINDINGS IN:

THE HANDS

Figure 34 : Deformity of distal ends of radius and ulna, and of carpal bones. (Grade +++).

Figure 35 : Deformed distal ends of radius and ulna, carpal deformities and brachymetacarpaly. (Grade +++).

Figure 36 : Marked metacarpal shortening. (Grade +++).

Figure 37 : Generalised osteoarthrosis of the hand. (Grade +++).

THE SPINE

Figure 38 : Irregularity of superior and inferior surfaces of vertebral bodies with Schmorl's nodes.

Figure 39 : Posterior humping of the vertebral bodies.

Figure 40 : Generalised platyspondyly.

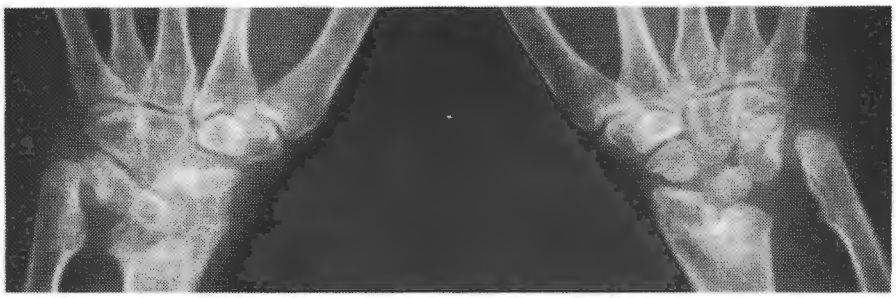


Fig.34:

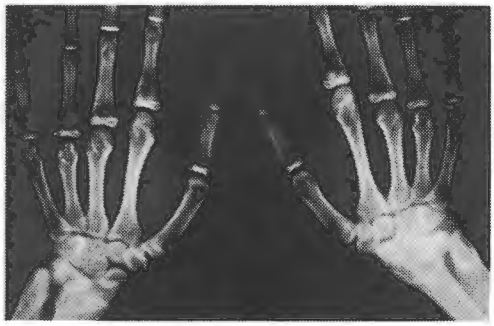
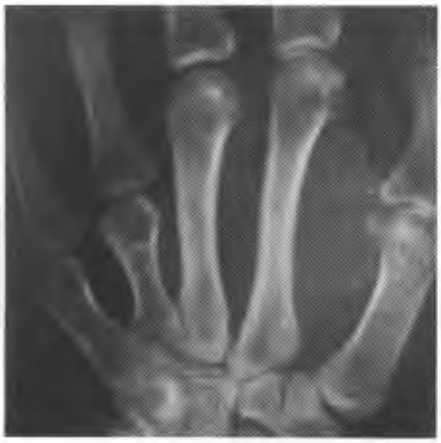


Fig. 35



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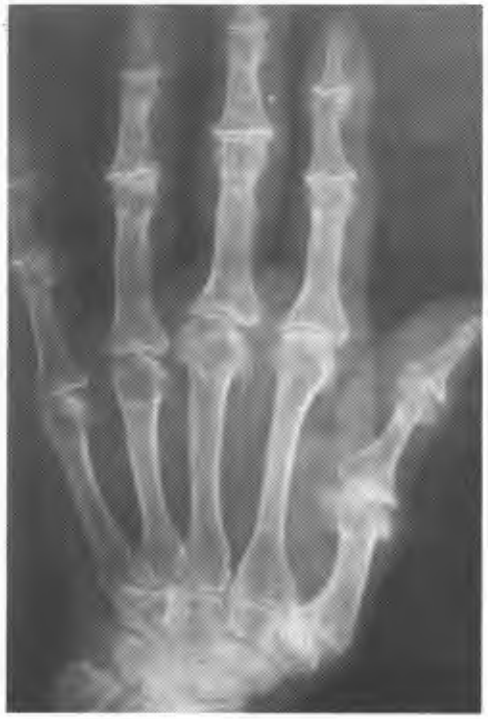

Fig. 37:

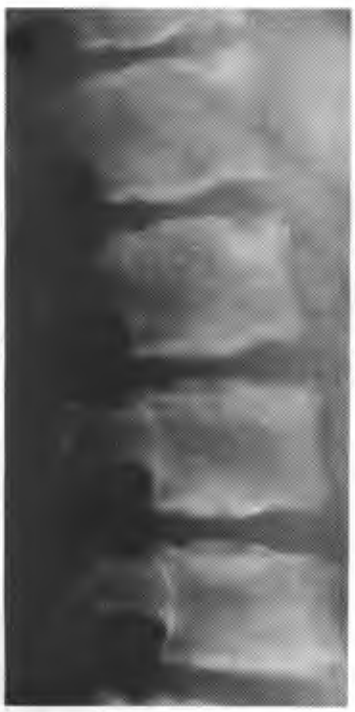

Fig. 38:

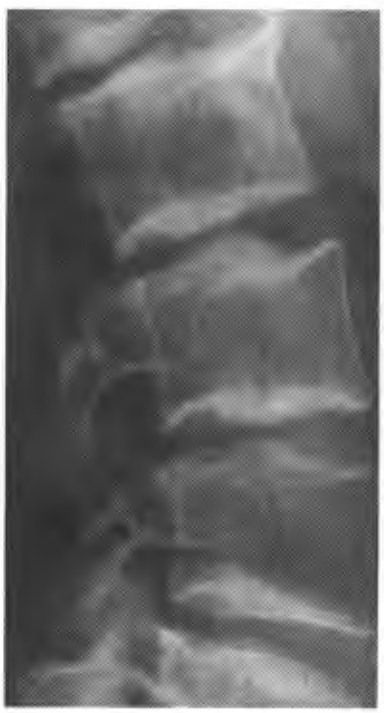

Fig.39:

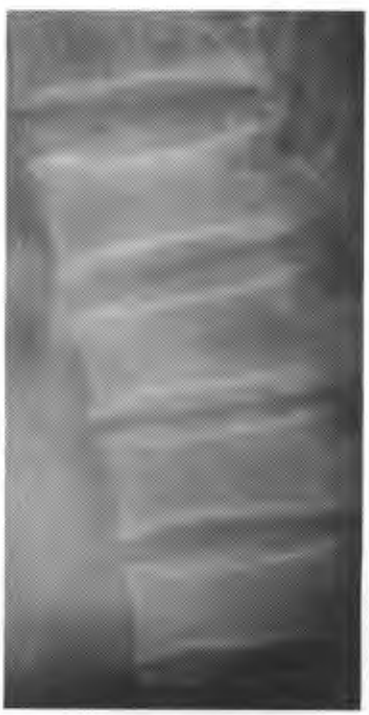

Fig. 40:

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In the severe osteoarthrosis there may be a fairly round femoral head usually associated with marked acetabular protrusion, or an obviously deformed femoral head often associated with a degree of subluxation. Fig. 21 illustrates osteoarthrosis with femoral head protrusion.

The knee in Mseleni Joint Disease

Mild dysplasia: The mild form of dysplasia is characterised by flattening of the femoral condyles and tiny areas of an osteochondritis dissecans-like appearance.

Moderate to severe dysplasia: This is characterised by moderate to marked irregularity of the articular surfaces of the tibia and the femur as is seen in Fig. 22. In some cases the head of fibula is flattened or mushroomed and in one case, hypoplasia of the fibula was seen.

Osteoarthrosis: The osteoarthritic appearance in the knee joint ranges from moderate joint space narrowing with osteophyte formation to almost total joint destruction. In Fig. 23 a severe (+++) degree of osteoarthrosis is seen.

The patella: A bipartite patella was seen in only 2 patients, and in one case a punctate mottling of the patella was seen. In over 200 patients the patella appeared to be normal.

The ankle in Mseleni Joint Disease

Mild changes: These are osteochondritis dissecans-like areas or defects seen on the medial or lateral superior aspects of the talus. See Fig. 24.

Moderate to severe dysplasia: This is characterised by lesser or greater degrees of irregularity of the articular surfaces of the talus and the tibia with occasionally a cystic appearance of the talus. (See Fig. 25). A slanting of the tibia and talus resulting in an oblique joint space or "tibial slant sign" is shown in Fig. 26.

Osteoarthrosis: As in the knee, the degenerative changes in the ankle range from moderately narrowed and irregular joint space to almost total obliteration of the joint. A typical example of a moderate severity (++) in the ankle is seen in Fig. 27.

The feet

Tarsals: Flattening and irregularity of the navicular bone is seen as in Fig. 28.

Metatarsals: Irregularity, notching and deformity of the metatarsal heads (See Fig. 29) ranges from mild to severe. Shortening of the 1st metatarsal ranges from mild to marked. An example of ++ shortening is seen in Fig. 28 and of +++ shortening in Fig. 31.

Osteoarthrosis: In Fig. 30 a generalised osteoarthrosis affecting meta-tarso-phalangeal, interphalangeal and intertarsal joints is seen.

Elbow

Dysplasia: This consists of irregularity of articular surfaces with deformity of the radial head.

Osteoarthrosis: Grades of moderate to severe osteoarthrosis are seen (See Fig. 33).

The shoulder

Dysplasia: This is characterised by flattening and irregularity of the humeral head.

Osteoarthrosis: Mild to severe osteoarthritic changes are seen as in Fig. 32).

The hand and wrist

Abnormality of the radius and ulna ranges from overgrowth to hypoplasia, with irregular articular surfaces and club or paddle type deformities. (Figs. 34 and 35).

Carpals: The carpal bones are small, irregular and deformed. Carpal fusions are noted in some cases, but this may be an incidental finding.

Metacarpals: Short metacarpals occur commonly, with the 1st, 4th and 5th metacarpals being most frequently affected.(Fig. 35,++, Fig. 36,+++).

Phalanges: Generally, there are no marked abnormalities.

Osteoarthrosis: Generalised osteoarthrosis affecting the radio-carpal, intercarpal, metacarpo-phalangeal and interphalangeal joint is seen. (See Fig. 37).

Spine

Mild degree: multiple Schmorl nodes.

Moderate to severe: The abnormalities include irregularity of the superior and inferior aspect of the vertebral bodies (Fig. 38) mild to severe vertebral flattening, and humping up of the vertebral bodies posteriorly on lateral view. (Figs. 39 and 40 respectively).

FREQUENCY OF THE VARIOUS RADIOLOGICAL ABNORMALITIES

Prevalence rates for the various radiological abnormalities in the population of the high prevalence area were obtained from the sample drawn for the multiple family unit studies. A random sample of adult women was drawn. Each woman with her husband and all available children over 8 years formed a complete family unit for the purpose of the study. Women whose husbands were dead or out of the area, or who had no children over 8 years were discarded from the sample. The sample is therefore, strictly speaking, a random sample of women with a husband present and at least one child over 8 years. For the purpose of obtaining prevalence figures for the radiological abnormalities, the women and their husbands alone formed the sample. No children, even though adult, was included. By excluding women with children only under 8 years a bias towards older women would have been introduced, but the exclusion of women whose husbands were dead would tend to bias the sample in the opposite direction. Thus although not strictly a random sample, it is presumably a reasonable reflection of the population, which will provide a fair estimate of radiological prevalence rates.

When more than one woman was married to a particular man, the findings for each woman were included but those for the man were considered only once. Hence this sample of 242 consists of 111 men and 131 women. Although it is a sample of people from the affected area for convenience it will be designated the Mseleni sample in contrast to the Sibaya sample, a random sample of 82 adults from the control area.

The Sibaya sample consisted of 82 adults from Sibiya sections 7 and 8 which served as a control area. The population in this area is of identical ethnic descent to that of the high prevalence area and the way of life is generally similar.

As a further comparison, radiographs from Bantu patients seen at the H. F. Verwoerd Hospital in Pretoria were examined. These consisted of hip, feet and hand plates drawn sequentially.

An arbitrary date was chosen 3 months previous to the time the plates were selected. Working sequentially, from the register of the X-ray department in which each radiograph is recorded, the number of each hip, foot and hand radiograph was noted until 100 of each joint had been obtained. These radiographs were then screened by the author. Only cases over 18 years were included. For obvious reasons, unlike the other two groups of radiographs, the hip, feet and hand plates were all from different people in most cases.

Patients who were referred to this X-ray department were from casualty, out-patients and wards, and included all disciplines. The radiographs were unselected other than that they had been taken sequentially.[43] Reasons for radiographic examination ranged from injuries to skeletal surveys for suspected neoplastic secondaries.

TABLE XVI NUMBER OF PEOPLE IN EACH SEX EXAMINED IN THE THREE GROUPS

	High prevalence area	Control area	Pretoria		
			Hips	Feet	Hands
Males	111	21	30	58	57
Females	131	61	30	12	13
Total	242	82	60	70	70

RESULTS:

The frequency of the findings in Mseleni and Sibaya samples are shown for the hips, hands and feet in Tables XVII, XXI and XX respectively. The findings in the knees, and ankles of the high prevalence group are shown in Table XVIII and in the spine in Table XIX.

THE FINDINGS IN THE PRETORIA SAMPLE ARE BRIEFLY SUMMARISED BELOW

Abnormalities relating to the reason for referral for X-ray, such as fractures will not be mentioned as they are not of interest here, unless the referral reason was for an arthritic condition.

HIPS

Sixty pelvic radiographs were seen, half were of females. Nine of the patients had significant protrusio acetabulae equivalent to that recorded in the Mseleni patients as grade 2. All were females. Three were between 20 and 25 years, one 30 and one 40 years old and the other four were 50 years or more. One of these women had slight joint space narrowing but no other indication of degenerative joint changes. The remaining 51 hips were normal from the point of view of the survey in that they showed none of the abnormalities seen in the Mseleni population. There was, therefore, a frequency of protrusio acetabuli of 30% among the women.

FEET

Plates were seen of 70 patients, of one foot only per patient for all but 2 cases. No example of metatarsal or tarsal dysplasia, or of generalised osteoarthrosis were seen. One male of 59 showed early osteo-

arthritic changes in the 1st metatarso-phalangeal joint. In 31 cases a moderate degree of shortening of the first metatarsal was present equivalent to a grade I shortening, as seen in the Mseleni patients. One male of 36 had a significant grade 2 shortening.

HANDS

Radiographs of 70 cases were seen, 57 were males and in most cases only a single hand was radiographed. No cases of radio-ulnar, carpal, or metacarpal dysplasia were seen, and there were no example of generalised osteoarthritis. The only abnormalities detected were a short 4th metacarpal in a man of 30, and a lunato-triquetral fusion in a man of 40. As only one hand had been examined in both cases, whether this was unilateral or bilateral is unknown.

TABLE XVII : NUMBER AND PERCENTAGE OF SUBJECTS CLASSIFIED INTO A SPECIFIC CATEGORY BASED ON RADIOLOGICAL FINDINGS IN THE HIP JOINTS (MSELENI AND SIBAYA SAMPLES)

No	Radiological category.	Random family unit sample			Sibaya random sample		
		Male	Female	Total	Male	Female	Total
1	Epiphyseal dysplasia	7 6,42	7 5,43	14 5,88	0	0	0
2	Dysplasia and protrusio	1 0,92	5 3,88	6 2,52	0	0	0
3	Dysplasia and osteoarthrosis	5 4,59	20 15,50	25 10,50	0	3 5,26	3 3,90
4	Dysplasia, Protrusio, osteoarthrosis	0	1 0,78	1 0,42	0	2 3,51	2 2,60
5	Osteoarthrosis	4 3,67	13 10,08	17 7,14	1 5,00	1 1,75	2 2,60
6	Osteoarthrosis and protrusio	0	14 10,85	14 5,88	0	1 1,75	1 1,30
	Total categories 1 - 6	17 15,60	60 46,5	77 32,25	1 5,00	7 22,81	8 10,39
7	Protrusio only Mild Grade 2	17 15,60	21 16,28	38 15,97	4 20,00	18 31,58	22 28,57
8	Protrusio only Moderate Grade 3	1 0,92	7 5,43	8 3,36	0	2 3,51	2 2,60
9	Protrusio with joint space narrowing	0	6 4,65	6 2,52	0	0	0
10	Minimal OA (Grade 1 Kellgren)	1 0,92	2 1,55	3 1,26	0	0	0
11	Shallow acetabulum	5 4,59	2 1,55	7 2,94	0	0	0
12	Normal	68 62,38	31 24,03	99 41,60	15 75,00	30 52,63	45 58,44
Total examined:		109	129	238	20	57	77

TABLE XVIII : NUMBER AND PERCENTAGE OF SUBJECTS CLASSIFIED INTO A SPECIFIC CATEGORY BASED ON RADIOLOGICAL FINDINGS IN THE KNEE AND ANKLE (MSELENI SAMPLE)

No.	Radiological category	Knee			Ankle		
		Males	Females	Total	Males	Females	Total
1	Epiphyseal Dysplasia	8 7,27	24 18,75	32 13,45	9 8,49	20 15,75	29 12,45
2	Metaphyseal flaring (knee only)	1 0,90	1 0,78	2 0,84	0	0	0
3	Slant sign (ankle only)	0	0	0	1 0,94	1 0,79	2 0,86
4	Dysplasia and osteo-arthrosis	1 0,90	2 1,56	3 1,26	0	4 3,15	4 1,72
5	Osteoarthrosis	1 0,90	13 10,16	14 5,88	1 0,94	18 14,17	19 8,15
6	Osteochondritis dissecans	0	0	0	3 2,83	0	3 1,29
7	Dysplasia with osteo-chondritis (ankles)	0	0	0	1 0,94	1 0,79	2 0,86
8	Dysplasia with fibula overgrowth (knee)	0	1 0,78	1 0,42	0	0	0
	Total in categories 1 - 8	11 10,00	41 32,03	52 21,85	15 14,15	44 34,65	59 25,32
	Bipartite patella	1 0,90	0	1 0,42	0	0	0
	Normal	98 89,09	87 67,97	185 77,73	91 85,85	83 65,35	174 74,68
	TOTAL:	110	128	238	106	127	233

TABLE XIX : NUMBER AND PERCENTAGE OF PATIENTS CLASSIFIED INTO A SPECIFIC CATEGORY BASED ON RADIOLOGICAL FINDINGS IN THE SPINE (MSELENI SAMPLE)

	Radiological category	Males	Females	Total
1	Mild vertebral flattening	6 5,83	1 0,80	7 3,07
2	Irregularity of vertebral end plates	0	2 1,60	2 0,88
3	Multiple Schmorl nodes	3 2,91	7 5,60	10 4,39
4	Flattening, irregularity and posterior humping	5 4,85	13 10,40	18 7,89
	Total in categories 1-4	14 13,59	23 18,40	37 16,23
5	Mild disc degeneration	19 18,45	6 4,80	25 10,96
6	Moderate disc degeneration	14 13,59	1 0,80	15 6,58
7	Total in categories 5 and 6	33 31,94	7 5,60	40 17,54
	Normal	56 54,37	95 76,00	151 66,23
	Total: Categories 1 - 7	103	125	228

TABLE XX : NUMBER AND PERCENTAGE OF PATIENTS CLASSIFIED IN SPECIFIC CATEGORIES BASED ON RADIOLOGICAL FINDINGS IN THE FEET.

(MSELENI AND SIBAYA SAMPLES)

	Radiological category	Male	Female	Total	Male	Female	Total
1	Tarsal and/or metatarsal dysplasia.	9 8,9	2 1,6	11 4,9	1 5,0	1 1,7	2 2,4
2	Dysplasia and short metatarsals.	10 9,9	8 6,5	18 8,0	0	0	0
3	Generalised osteoarthrosis.	0	9 7,3	9 4,0	0	1 1,7	1 1,3
4	Generalised osteoarthrosis and dysplasia.	0	3 2,4	3 1,3	0	0	0
5	Generalised osteoarthrosis and short metatarsals	0	4 3,3	4 1,8	0	0	0
6	Dysplasia, osteoarthrosis short metatarsals	0	1 0,8	1 0,5	0	0	0
	Total categories 1 - 6	19 18,8	27 22,0	46 20,5	1 5,0	2 3,3	3 3,8
7	Short 1st metatarsal	26 25,7	24 19,5	50 22,3	6 30,0	8 13,3	14 17,5
8	Stunted 1st metatarsal	10 9,9	8 6,5	18 8,0	2 10,0	1 1,7	3 3,8
9	Multiple short metatarsals	0	1 0,8	1 0,5	0	1 1,7	1 1,3
10	Osteoarthrosis of the 1st metatarsal phalangeal joint only	4 4,0	6 4,9	10 4,5	1 5,0	5 8,3	6 7,5
11	OA 1st metatarsal and short metatarsal	0	6 4,9	6 2,7	1 5,0	1 1,7	2 2,4
12	Normal	42 41,6	51 41,5	93 41,5	9 45,0	42 70,0	51 63,8
	TOTAL:	101	123	224	20	60	80

TABLE XXI : NUMBER AND PERCENTAGE OF PATIENTS IN A SPECIFIC CATEGORY BASED ON RADIOLOGICAL FINDINGS IN THE HANDS (MSELENI AND SIBAYA SAMPLE)

		Mseleni Sample			Sibaya Sample		
	Radiological Category	Male	Female	Total	Male	Female	Total
1	Irregularity or deformity of radius and/or ulna	16 14,4	20 15,5	36 15,0	0	2 3,3	2 2,4
2	Carpal deformities	1 0,9	6 4,7	7 2,9	0	1 1,6	1 1,2
3	Generalised osteoarthrosis	1 0,9	6 4,7	7 2,9	0 0,0	0 0,0	0 0,0
4	Multiple deformities of carpals, radius ulna or metacarpals	2 1,8	5 3,9	7 2,9	0 0,0	0 0,0	0 0,0
5	Osteoarthrosis with carpal deformities or short metacarpals	1 0,9	3 2,3	4 1,7	0 0,0	0 0,0	0 0,0
	Total categories 1 - 5	21 18,9	40 31,0	61 25,4	0 0,0	3 4,8	3 3,7
6	Short metacarpals Gr. 1	20 18,0	7 5,4	27 11,3	2 9,5	0 0,0	1 1,2
7	Short metacarpals Gr. 2	2 1,8	0 0,0	2 0,8	0 0,0	0 0,0	0 0,0
8	Carpal fusions	3 2,7	5 3,9	8 3,3	2 9,5	1 1,6	3 3,7
9	Phalangeal abnormalities	8 7,2	5 3,9	13 5,4	2 9,5	1 1,6	3 3,7
10	Normal	57 51,4	72 55,8	129 53,8	15 71,4	56 91,8	68 82,9
	Total	111	129	240	21	61	82

DISCUSSION OF PREVALENCE FIGURES

THE HIP JOINTS (The results are presented in Table XVII)

On the assumption that the basic pathology in MJD is a form of epiphyseal dysplasia progressing to osteoarthrosis, categories 1 to 6, including all persons with either dysplasia or established osteoarthrosis, have been grouped together as "affected". It can be seen that in the Mseleni sample 15,60% of the men and 46,50% of the females are affected as opposed to 5% of the Sibaya men and 22,8% of the Sibaya women. When the total adult sample is considered, 32,21% of the family unit sample and 10,39% of the Sibaya sample are affected.

The significance of protrusio acetabulae in the Mseleni population can be considered here. In the Mseleni sample, 19 men (17,4%) and 40 women (31,02%) had significant protrusio acetabulae. However, in the Mseleni sample, in 18 men (16,5%) and 34 women (26,4%) this was an isolated finding. In the Sibaya sample, the figures were 4 (24%) and 20 (35,1%) for men and women respectively. Among the 30 Pretoria males there was no significant protrusio acetabuli but it was present in 9 (30%) of the women. Beighton and Solomon[17] in a survey of 175 Tswana women over 45 years of age, found a prevalence rate for protrusio acetabuli of 13%. Crichton and Curlewis[41] compared radiographs of a series of Bantu and European females referred for pelvimetry. They found an incidence of 25,7% among the Bantu, 5,7% among the Indians and 2,9% among the Europeans.

Since a high incidence of protrusio acetabuli appears thus to be not restricted to the Mseleni population, it is probably not of significance in MJD.

There were 7 people in the Mseleni sample with a slightly shallow acetabulum but no marked subluxation of the femoral head was seen.

THE KNEE JOINT (See table XVIII)

Radiographs of the knee were available for 238 of the people in the Mseleni sample. Ten percent of the men and 32% of the women had either epiphyseal dysplasia or osteoarthrosis of the knee joint. Metaphyseal flaring was noted in two subjects only and both were found to be dwarfs.

THE ANKLE JOINT (See Table XVIII)

Radiographs of the ankle were obtained for 233 of the people in the Mseleni sample. Fourteen percent of the men and almost 35% of the women had epiphyseal dysplasia, osteochondritis or osteoarthrosis of the ankle joint. "Slant sign" was present in two subjects. These were dwarfs.

THE SPINE

The results are presented in Table XIX. Radiographs of the spine were obtained for 103 men and 125 women of the Mseleni sample. Categories 1 to 4 include the characteristics commonly found in the multiple and spondylo-epiphyseal dysplasias. It can be seen that 13,59% of the men and 18,40%of the women show these characteristics.

The relationship of the degenerative changes in the spine such as disc narrowing and anterior osteophytes is not altogether clear. However, unlike the other abnormal findings, this was far more common in men than in the women. Spinal degenerative changes were noted commonly in people with no obvious osteoarthrosis or dysplasia in other joints.

Kellgren and Lawrence[87] in a survey of osteoarthrosis in a random sample of people in the age group 55 to 64 years in Leigh, found disc degeneration occurred more commonly in males than females. It is therefore probable that in many of the 17% of patients with disc degeneration, this finding is a "wear and tear" form of osteoarthrosis and not due to MJD.

If those people in categories 1 - 4 are considered as affected the prevalence for MJD of the spine is almost equivalent to that for the hip, knee and ankle with regard to the men but somewhat lower with regard to the women.

THE FEET

The results are shown in Table XX. Radiographs of the feet were obtained for 224 people from the Mseleni sample, and 80 people of the Sibaya sample. There was some doubt at first whether people with short metatarsals as an isolated anomaly were affected by MJD. However, while 30% of the Mseleni group had brachymetatarsaly as the only abnormality in the foot, so did 21% of the Sibaya group and 32,7% of the Pretoria sample.

Similarly, osteoarthrosis of the 1st metatarso-phalangeal joint was noted in 9,8% of the Mseleni sample and 9,9% of the Sibaya group. This was seen only in 1,5% of the Pretoria group but as the finding was often unilateral, and only one foot was examined for most of the Pretoria subjects, it is possible that some were missed.

Kellgren and Lawrence[87] in their survey of the 55 to 64 year subjects found that the first metatarso-phalangeal joint together with the distal interphalangeal joints of the fingers were the joints most frequently affected by osteoarthrosis in both sexes. It is possible that the patients with osteoarthrosis of the first metatarsal joint or short metatarsals as the only anomaly in the foot should not be included as showing MJD in the foot.

Those with the stigmata of MJD in the foot, will therefore include those with generalised osteoarthrosis or dysplasia of the metatarsals or tarsals. This represents almost 19% of the men and 22% of the women in the Mseleni sample, 5% of the men and 3% of the women in the Sibaya sample, and none in the Pretoria sample.

THE HANDS

The findings are shown in Table XXI. Abnormalities in the hand considered to be part of the Mseleni syndrome included generalised osteoarthrosis involving the carpal bones, metacarpo-phalangeal and interphalangeal joints, or deformity of the carpals or distal ends of radius and ulna.

A minor degree of metacarpal shortening was seen in 11% of the Mseleni sample and 1% of the Sibaya sample, and is probably not a part of the Mseleni syndrome. One male with a short metacarpal was noted in the Pretoria group. Carpal fusions were found in 3% of the Mseleni sample and 3% of the Sibaya sample. This conforms to the prevalence of 4,6% found by Levine[105] in his study of carpal fusions among Pretoria school children of four racial groups. In all but one of the 11 instances of fusions were lunato triquetral and one was of the hamate and capitate. A single instance of lunato triquetral fusion was also seen in the Pretoria Group.

Comparison of census prevalence figures with radiological figures

A higher percentage of affected women than affected men was seen for each joint examined. This reflects the findings in the enumeration. However, this difference might reflect bias in sampling as discussed in section II.4.5.

It may be seen that the radiological prevalence findings were somewhat higher than those obtained in the 1973 census for the high prevalence area. If the hip joint is considered the following comparison may be made regarding affected people:

	1970 enumeration.	Mseleni radiological prevalence	1973 enumeration
Adult males	29,7	15,60%	15,9%
Adult females	66,7	46,5%	32,9%

Therefore, while the 1973 enumeration appeared to reflect the prevalence rate among men, the estimates of prevalence among women were

lower than the actual rates. However, a definite radiological prevalence rate awaits the completion of the serogenetic survey calculation as this was based on as random a sample as is possible to obtain in this area.

Summary of radiological findings

The most marked feature of Mseleni Joint Disease is the marked heterogeneity. For each type of joint there has been defined several basic types of abnormality. Within each type there is a wide variation in form and severity. These types of abnormality are listed for each joint.

Hip joint:

1. Dysplasia of the femoral head - irregularity of outline or density;
   - distortion of shape, mushrooming, hatchet-shaped.
2. Dysplasia with early secondary osteoarthrosis;
3. Advanced osteoarthrosis - with relatively normal femoral head;
   - with grossly deformed femoral head;
   - with rounded head and gross acetabular protrusion.

Knee joint:

1. Osteochondritis dissecans: multiple foci.
2. Dysplasia of articular surfaces - condylar flattening
   - irregularity
   - metaphyseal flaring and irregularity.
3. Dysplasia with early secondary osteoarthrosis.
4. Advanced osteoarthrosis.

Ankle joint:

1. Osteochondritis dissecans - multiple foci.
2. Dysplasia - irregularity of articular surfaces.
3. Slant sign - marked slanting of the articular surfaces of talus and tibia.
4. Dysplasia with early secondary osteoarthrosis.
5. Advanced osteoarthrosis.

Feet:

1. Dysplasia of the metatarsal heads.
2. Deformities of the tarsal bones.
3. Generalised osteoarthrosis.

Shoulder:

1. Dysplasia - flattening and irregularity of humeral head.
2. Dysplasia with early secondary osteoarthrosis.
3. Advanced osteoarthrosis.

Elbow:

1. Dysplasia - flattened or mushroomed radial head.
2. Dysplasia with early secondary osteoarthrosis.
3. Advanced osteoarthrosis.

Hands:

1. Dysplasia - irregularity or deformity of the phalangeal heads;

- irregularity of the metacarpal heads;
- marked stunting of the metacarpals;
- deformity of the carpal bones;
- deformity and abnormalities of length of the radius or ulna

2. Dysplasia with early secondary osteoarthrosis.
3. Generalised osteoarthrosis.

Spine:

1. Irregularity of anterior and superior rims of vertebral bodies.
2. Multiple notches resembling Scheuermann's disease.
3. Platyspondyly - mild to severe;
   - localised to generalised.
4. Anterior wedging or tonguing.
5. Posterior humping.
6. Disc degeneration with osteophytosis.

These various elements of the disease were combined in various ways to form a wide spectrum of findings amongst the population. In general, while the younger patients had epiphyseal dysplasia in multiple joints symmetrical, severe multiplex osteoarthrosis was found among older patients. However, fairly advanced osteoarthrosis was seen in one or two joints of the younger patients while several elderly people with marked osteoarthrosis in the hips or knees had obvious epiphyseal dysplasia in the hands or shoulders.

The spinal involvement was extremely variable.

Many of the younger patients had irregularity, notching, platyspondyly, wedging or even posterior humping while in other cases with dysplasia in multiple joints, the spine appeared to be completely normal. The same can be said for the older patients. A few cases were seen with dysplasia in the hands and feet alone.

The dwarfs were characterised by a more marked degree of epiphyseal dysplasia, often wide flared metaphyses, and very short thick metacarpals and metatarsals. All but 5 showed platyspondyly; in 1 the spine was completely normal.

DIFFERENTIAL DIAGNOSIS OF MSELENI JOINT DISEASE

It is apparent from the radiological and clinical work in the preceding section that the predominant abnormality giving rise to the symptomatology of MJD is a severe disabling multiplex osteoarthrosis. It is well recognised however that the diagnosis of osteoarthrosis is not sufficient in itself and that a predisposing cause should always be sought [65, 151]. While the severe epiphyseal abnormalities seen in many of the Mseleni pictures would indeed strongly predispose to the development of osteoarthrosis , it is well to consider whether there are any other factors which may be implicated.

During the period that MJD has been under investigation, a great many interested colleagues have proposed possible diagnoses for this disorder. Several conditions have repeatedly been suggested as they are known to give rise to severe disabling osteoarthrosis. Some of those factors which must be considered in the pathogenesis of degenerative joint disease will be briefly reviewed in relation to the Mseleni situation.

Osteoarthrosis has been defined by Kellgren[88] as the expression of a joint's inadequacy to meet the mechanical stress placed upon it. This inadequacy may occur as a secondary phenomenon in a previously damaged or abnormal joint or it may be a primary phenomenon in an apparently normal joint.

Primary osteoarthrosis is that which develops in an apparently normal joint, while secondary osteoarthrosis is that which develops in a joint which is already abnormal. This abnormality may be due to trauma, asep-

tic necrosis, e.g. caisson disease, osteochondritis; primary acetabular protrusion, inflammatory disorders e.g. rheumatoid arthritis and brucellosis, familial factors e.g. hypermobility, alcaptonuria, haemochromatosis, or the hereditary bone dysplasias, endocrinopathies e.g. hypothyroidism and acromegaly, environmental factors, e.g. Kashin-Beck disease which may be due to ingestion of grain infested by the fungus fusarium sporotrichiella, as well as other causes. Many of these conditions could obviously not be implicated as a cause of generalised osteoarthrosis among a population. There was no clinical evidence of acromegaly or obvious hypothyroidism. Trauma would be an unlikely cause of generalised osteoarthrosis, as would pyogenic and tubercular arthritis, both of which would most likely affect a single joint.

Rheumatoid arthritis is known to be rare in the rural African[16] and the tests for rheumatoid factor in the clinical survey were negative in all the patients tested[29] . However, this condition had still to be considered as a possible cause of MJD.

Brucellosis was suggested as a possible cause of MJD. However, on both clinical and radiological grounds it was considered unlikely that Brucellosis was of aetiological significance in MJD. As confirmatory evidence tests for brucellosis antibodies were carried out in sera of affected people from Mseleni and were found to be negative[94] .

Although abnormal iron storage disorders such as haemachromatosis may result in arthropathy, the manifestation of these conditions are very different from the stigmata of MJD. Serum iron and transferrin values were normal in the Mseleni population[29a] and both haemachromatosis and haemosiderosis

were thus excluded from further consideration.

Alkaptonuria, although a cause of degenerative arthropathy with a radiological appearance in the spine superficially resembling the vertebral humping of some Mseleni patients, is unlikely to be an aetiological factor in MJD. Disorder severe enough to cause an ochronotic arthropathy would probably manifest with back pain and with black urine before presenting as an osteoarthrosis of the hip.

Protrusio acetabuli is the term applied to a deformity of the pelvis in which the medial wall of the acetabulum bulges into the pelvis cavity with medial displacement of the femoral head. While protrusio acetabuli may result from recognised disease processes[60] a primary form with no associated disorder is well recognised.[77,113] Although this disorder predisposes to the development of osteoarthrosis, it could not result in degenerative changes in other joints such as the hands and shoulders. Furthermore, although primary protrusio acetabuli is seen frequently in the Mseleni population, it was equally prevalent in the Sibaya people, and indeed is recognised to occur with higher frequency among the Negroid races of South Africa.[17,41] This condition can obviously not be implicated as the sole predisposing factor in MJD although affected people may indeed develop osteoarthrosis of the hip.

As an example of a disease of presumed environmental aetiology which produces a disorder of generalised osteoarthrosis prevalent in a defined type of geographical area, Kashin Beck disease[14, 137] will be discussed in detail.

Kashin Beck disease is a chronic, disabling, generalised osteoarthrosis symmetrically involving mainly peripheral joints. It is endemic in Eastern Siberia, Northern China and Northern Korea.

This disease was known to be prevalent among the Cossacks of the Urov River region as long ago as 1840. It was first described by Kashin in 1861 ; the clinical picture and prevalence was described in 1906 by the Becks[14] . A review of the clinical aspects was published by Nesterov in 1964[137].

The disease is endemic in those parts of China, Korea and Russia characterised by a cold but snow-free winter, with hot wet summer. The ground is frozen to a great depth all year round and the soil in the low lying areas remains waterlogged[90a].

There is a gradual symmetrical thickening and deformity of the joints often with asymptomatic development in school age children. The inter-phalangeal and wrist joints are most commonly affected. Crepitus is present but signs of acute inflammation are not seen. Most patients complain of slight aching and muscular weakness, exacerbated by exertion.

The disease is slowly progressive but Nesterov[137] states that if a patient changes his place of residence and receives treatment during the early stage of the disease, progression of the disease may be halted.

The disease is classified into three stages.

During the early stages the patient may be asymptomatic or complain of pain, stiffness and rapid fatiguability. The physical findings are

enlargement of symmetrical joints of the extremities, most commonly the interphalangeal joints of the fingers, the wrists and the ankles. Crepitus is often noted in the knees.

Later increased pain and limitation of joint mobility is present and deforming osteoarthrosis of the interphalangeal, carpal, radio-ulnar, ankle and knee joints becomes marked.

In the late stages the general manifestations of chronic disease appear. These are muscular and general weakness, decreased joint mobility and decreased capacity for work. The patient may have a waddling gait, reduction of height, shortening of fingers and forearms. There is flattening of vertebral bodies with osteophytosis. Myocardopathy, chronic gastritis with hypoacidity, anaemia with lymphocytosis may be present. In general, life expectancy is not shortened, and sexual function is normal.

The aetiological factor is believed to be a toxin produced by a fungus fusarium sporotrichiella which is found on the bread grain grown under the specific climatical conditions described earlier. This theory received support from rat and puppy experiments where similar changes in the articular cartilage, epiphyses and metaphyses formed when the animals were fed grain contaminated by the fusarium. Furthermore, with the introduction of unaffected imported grains, the incidence apparently showed a decline.

This disorder has on several occasions been suggested as a possible cause of MJD, both conditions being characterised by a high prevalence of disabling osteoarthrosis within defined geographical areas. However,

Kashin Beck (K-B) disease may be differentiated from MJD on both climatic and clinical grounds.

The climate characteristic of the K-B endemic area is that of a cold winter with ground frozen deeply all year round very unlike the subtropical climate of Zululand.

The fungus fusarium sporotrichiella is a low temperature organism and it has not been recorded in the warmer climate of South Africa. The only recorded local area where this fungus has been observed is in the highlands of Lesotho[145].

Clinically the main lesions of K-B disease occur in the small joints of the hands and wrist while in MJD the hips are predominantly affected.

If indeed, fusarium sporotrichiella is a major factor in K-B disease, it is probably not implicated in MJD. However, the significance of K-B disease is that it is an example of an possible environmental cause for a disease in many ways resembling MJD.

Primary osteoarthrosis is by definition, that which occur in an apparently normal joint. Kellgren and Lawrence[91] suggested that primary generalised osteoarthrosis associated with Heberden's nodes was an inherited characteristic possibly due to a constitutional abnormality of articular cartilage.

Kellgren[88] stated that in this primary generalised form of osteoarthrosis the hip is rarely affected, but that osteoarthrosis of the hip and other joints with multiple disc degeneration in the spine occurs fre-

quentlyin the group of familial diseases classified as chondrodystrophy or epiphyseal dysplasia.

The joints involved in the Mseleni patients are predominantly the hips, knees and ankles although the smaller joints are often involved as well. This particular joint distribution resembles that of the epiphyseal dysplasias rather than that of primary generalised osteoarthrosis.

CONCLUSION FROM THE RADIOLOGICAL SURVEY

The end stage of MJD, seen in elderly patients is clearly a disabling osteoarthrosis of multiple joints. The most probable predisposing factor is the anatomical derangement of the joints by a form of epiphyseal dysplasia.

II.2.4 A RADIOLOGICAL STUDY OF THE MEMBERS OF FIVE GENEALOGIES

III.2.4: A RADIOLOGICAL STUDY OF THE MEMBERS OF FIVE GENEALOGIES

Objectives: The object of this study was to investigate possible modes of inheritance of MJD by multiple pedigree analysis.

Methods: Five extended families were selected for study by the propositus method. Detailed family histories had been obtained from at least one person in each kraal in the affected area. During analysis of family histories obtained from the dwarfs, it was found that most of the dwarfs were related to at least one other of the dwarfs and to several other affected people. Five extended families with at least two dwarfs from different but related family units were finally selected for study in depth. The dwarf propositi from 3 of these families are shown in Figs. 41, 42 and 43). Genealogies were constructed from the family histories by the author who then checked and cross-checked by interviewing as many of the adult members of the families as possible. Then every person in each genealogy, over 10 years of age, who was available for examination was radiologically examined. A total of 315 people were examined and over 2000 films of all the major joints were seen. For each person a complete examination included AP-views of hips, knees, ankles, hands, wrists and feet, and a lateral X-ray of the lower thoracic and lumbar spine. AP-views of shoulders and elbows were done in most people with symptoms of joint pain. For each dwarf every joint mentioned above was radiographed and a lateral and PA-view of skull was also done.

Fig. 41: Dwarfs from Genealogy I: Propositus III 53, his sister III 58, and first cousin III 36.

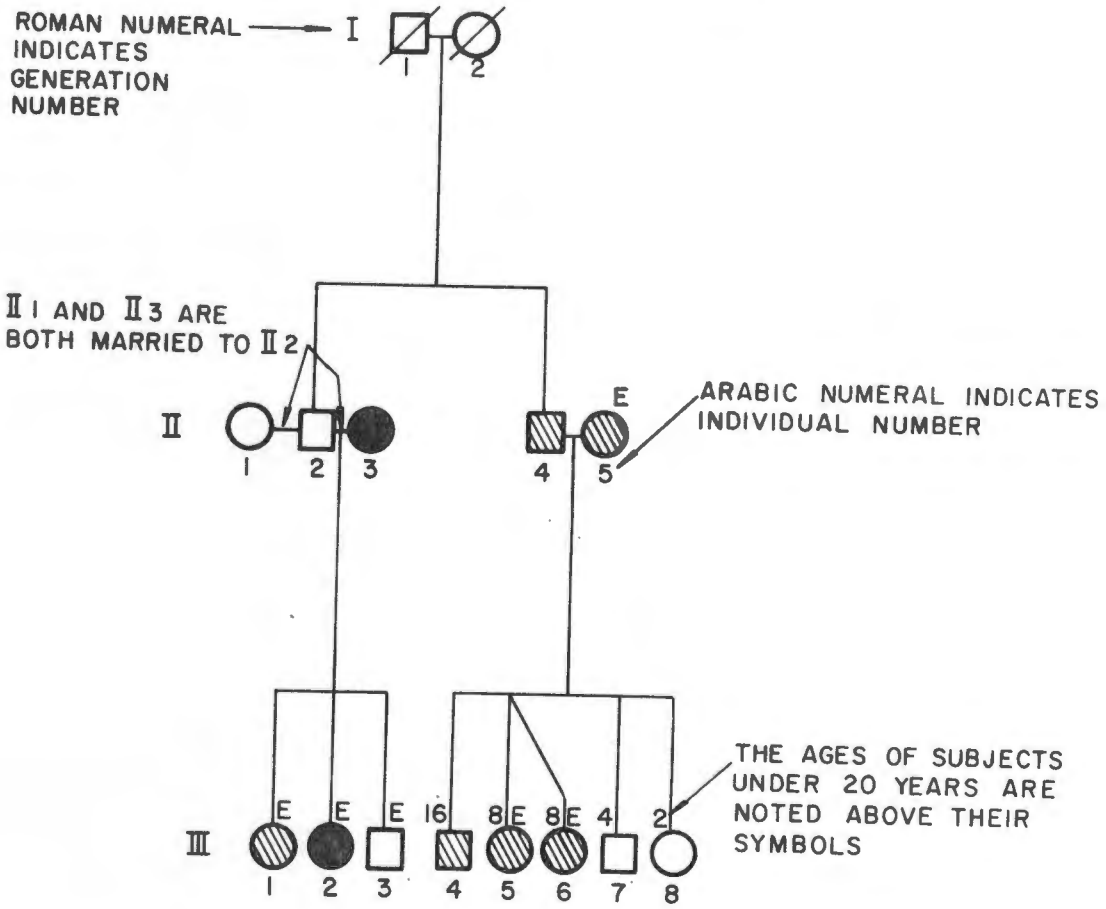
Fig. 42: Dwarfs from Genealogy 3: Propositus III 19 (118 cms) and her mother, also dwarfed *(on left)*

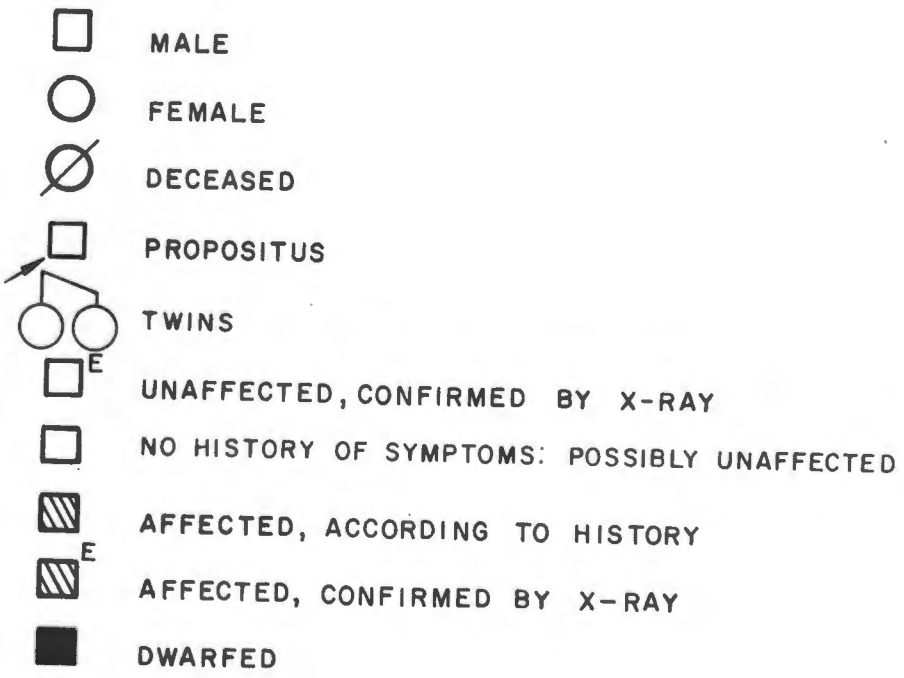
Fig. 43: Dwarfs from Genealogy 2.
Propositus IV 2
IV 33 and
III 7.

GAcsir01HL2172*174

FIGURE 44

DIAGRAM TO SHOW FORMAT USED IN THE GENEALOGICAL CHARTS





RG4-6925

Results: Each of the five genealogies is described and analysed individually and the composite findings are then discussed. The format used in the genealogical diagrams may be seen from Fig. 44. In the discussion the term "MJD status" refers to whether or not the subject discussed is affected by MJD or not. MJD positive indicates an affected person, while MJD negative indicates that the person is unaffected.

GENEALOGY I : THE MAPHANGA FAMILY (Fig. 45).

This genealogy illustrates the relationship and disease of the descendants of 3 brothers, a sister and a half-sister II(4), II(11), II(16), II(19) and II(21) all of whom are now dead.

This extended family was selected for investigation when the two independently ascertained dwarf propositi, persons III(36) and III(53) were found to be first cousins. Nothing is known about the disease status of Generation I. II(16) is said to have been under 5 ft (152 cms) and both II(19) and II(21) are said by several people to have been affected by joint disease. Conflicting statements were made as to the MJD status of II(4) and II(11) but both were said to be tall men and it is probable that they were unaffected though their MJD status remains uncertain. The mother of affected person III(16), deserted her in infancy and the MJD status of the mother is unknown.

A total of 63 adults in generations III and IV were examined radiologically. This included both direct descendants and their spouses. It can be seen that at least 6 affected women and 1 dwarfed male married into this family. Two of the women are members of the second major

FIGURE 45

GENEALOGY I: THE MAPHANGA FAMILY

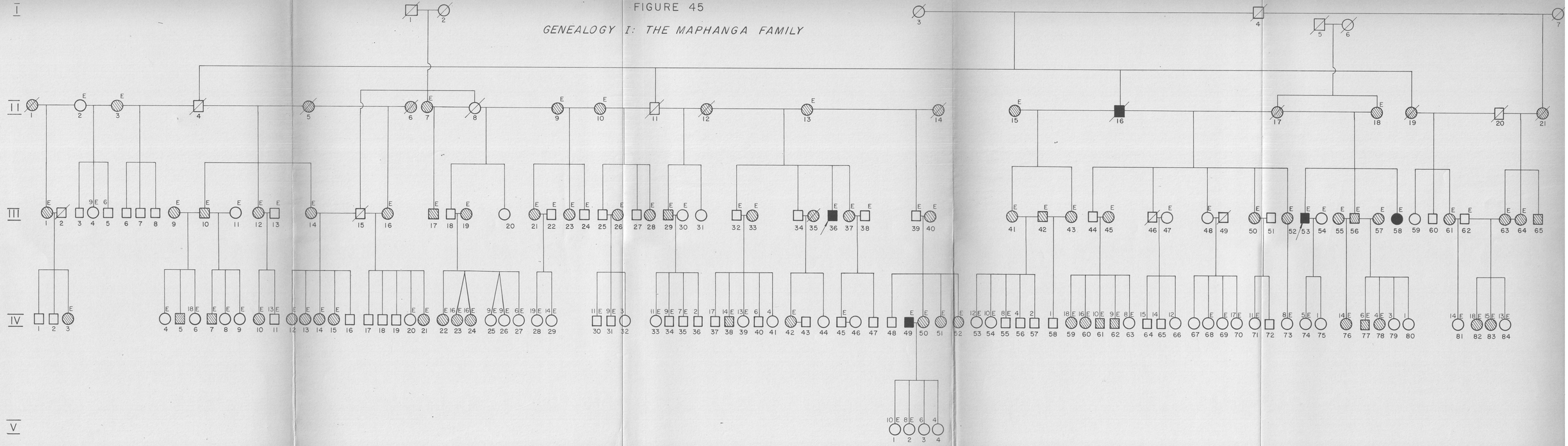


TABLE XXII : ANALYSIS OF FAMILY UNITS FROM GENEALOGY 1

Parents				Children											
Identification		Disease status		Not examined radiologically					Examined radiologically						
No of husband	No of wife.	Husband	Wife	8 years or less	Away-unsure Male	Away-unsure Female	Affected on history Male	Affected on history Female	Normal Male	Normal Female	Affected Male	Affected Female	Total examined	Total
1 III 10	III 9	Afft.	Afft.				1			2			2	3
2 III 10	111 11	Afft.	Normal							2	1		3	3
3 III 13	III 12	Normal	Afft.						1			1	2	2
4 III 22	III 21	Normal	Afft.							2			2	2
5 III 29	III 30	Afft.	Normal	1					2	1			3	4
6 III 32	III 33	Normal	Afft.	2	1					1	1		2	5
7 III 38	III 37	Normal	Afft.		1				1				1	2
8 III 39	III 40	Normal	Afft.		1							3	3	4
9 III 42	III 41	Afft.	Afft.	2					1	2			3	5
10 III 42	III 43	Afft.	Afft.	1									0	1
11 III 53	III 54	Afft.	Normal	2									0	2
12 III 56	III 55	Afft.	Afft.									1	1	1
13 III 56	III 57	Afft.	Afft.	2							1	1	2	4
14 III 62	III 61	Normal	Afft.							1			1	1
15 III 62	III 63	Normal	Afft.							1		2	3	3
16 III 62	III 64	Normal	Afft.										0	0
17 IV 49	V 50	Afft.	Afft.	2						2			2	4
TOTAL:				12	3		1		5	14	3	8	30	46

TABLE XXIII : AFFECTED PEOPLE FROM GENEALOGY 1 (ARRANGED BY FAMILY UNITS) SHOWING DEGREE OF ABNORMALITY IN EACH JOINT AS SEEN ON RADIOLOGICAL EXAMINATION

No.	Patient No.	Sex	Approx. age	Hips	Knees	Ankles	Feet	Hands	Elbows	Shoulders	Spine	Relationship
1	II 3	F	60	+++	++	0	0	++	0	0	0	
2	II 7	F	60	+++	+++	++	++	++	++	0	0	
3	III 17	M	30	+++	+++	+++	+++	+++	-	-	+	Son of 2
4	II 9	F	55	+++	+++	+	+++	++	+++	++	+	
5	III 21	F	45	++	+	-	++	-	+++	-	-	Daughter of 4
6	III 23	F	30	++	+	-	-	-	0	0	-	Daughter of 4
7	II 10	F	60	+++	+++	+	+	+++	+++	+++	-	
8	III 28	F	30	++	+	++	+	++	0	0	+++	Daughter of 7
9	II 13	F	60	+++	0	0	+	+++	0	0	+	
10	III 36	M	30	+++	+++	+++	+++	+++	+	+	+++	Son of 9
11	III 37	F	40	++	-	-	0	-	-	-	-	Daughter of 9
12	II 15	F	65	+++	++	0	0	+++	0	0	0	
13	III 41	F	45	+++	+	+	0	+	-	0	0	Daughter of 12
14	III 42	M	50	++	-	-	-	-	-	-	-	Husband of 13&15
15	III 43	F	40	++	+	+	0	+	+	-	++	Daughter of 12
16	II 18	F	55	+++	+++	+++	0	0	0	0	+	
17	III 53	M	30	+++	+++	+++	+++	+++	+	+	+++	Son of 16
18	III 56	M	40	+++	0	0	0	0	0	0	+++	Son of 16
19	III 55	F	35	+++	+++	+++	0	+++	0	0	+	Wife of 18
20	IV 76	F	14	+	-	-	0	-	0	0	-	Daughter of 19 and 18
21	III 57	F	30	+	+	+	0	+	0	0	+	Wife of 18
22	IV 77	M	6	+	-	-	0	-	0	0	-	Son of 21 & 18
23	IV 78	F	4	+	-	-	0	-	0	0	-	Daughter of 21 and 18
24	III 58	F	25	+++	+++	+++	+++	+++	0	0	+++	Daughter of 16
25	III 1	F	55	+++	+++	++	+	+++	+++	+	-	
26	IV 3	F	30	+++	+++	++	+	+	-	+	+++	Daughter of 25
27	III 9	F	90	+++	++	++	0	++	0	0	-	
28	III 10	M	45	-	-	-	+	+	0	0	-	
29	IV 7	M	20	+++	+	+++	+++	+++	-	-	+++	Son of 28
30	III 12	F	45	+++	++	+++	+	++	0	+	+	
31	IV 10	F	22	+++	+	++	++	++	-	-	-	Daughter of 30

\+ = Abnormal
++ = Markedly abnormal
+++ = Grossly abnormal
0 = No film available (radiograph)
\- = Normal.

(Continued on next page/.....

TABLE XXIII : (Cont.).

No.	Patient No.	Sex	Approx. age	Hips	Knees	Ankles	Feet	Hands.	Elbows	Shoulders	Spine	Relationship
32	IV 14	F	50	+++	+++	0	0	+++	+++	++	++	
33	IV 12	F	36	+++	+	+++	0	-	+	+	+	Daughter of 32
34	IV 13	F	30	+++	+	-	0	-	-	-	-	Daughter of 32
35	IV 14	F	26	+++	+++	-	+	-	-	-	+	Daughter of 32
36	IV 15	F	24	+	+	+	0	-	0	0	-	Daughter of 32
37	III 16	F	54	+++	+++	+++	0	+	-	+++	++	
38	IV 21	F	38	++	++	++	0	-	-	-	++	Daughter of 37
39	III 19	F	40	0	0	0	0	0	+++	-	0	
40	IV 22	F	20	+++	++	+++	+++	+	+	-	+++	Daughter of 39
41	IV 23	F	16	+	-	-	-	-	0	0	+	Daughter of 39
42	IV 24	F	16	+	++	-	++	+	-	-	+++	Daughter of 39
43	III 26	F	35	+++	-	+	+	+	0	0	++	
44	III 29	M	40	-	-	++	++	-	0	0	-	
45	III 33	F	40	++	-	-	0	-	-	-	-	
46	IV 38	M	12	-	-	++	++	-	0	0	-	Son of 45
47	III 40	F	50	+++	+	+	+	++	+	+	0	
48	IV 50	F	30	+++	++	++	0	+++	0	0	+++	Daughter of 47
49	IV 51	F	25	+	-	-	+	-	0	0	+	Daughter of 47
50	IV 52	F	20	+++	+++	+++	0	++	++	++	+++	Daughter of 47
51	III 42	M	50	+	0	0	0	-	-	-	0	
52	III 45	F	45	+++	++	+	0	++	-	+	-	
53	IV 59	F	18	+++	++	++	0	++	+	+	+++	Daughter of 52
54	IV 60	F	16	++	+	+	0	-	-	0	0	Daughter of 52
55	IV 61	M	10	+++	+++	+++	0	+++	0	+++	0	Son of 52
56	IV 62	M	9	++	++	+	++	-	+	-	0	Son of 52
57	III 50	F	45	-	-	++	0	-	-	-	-	
58	III 52	F	40	+++	+	-	-	-	-	-	+	Sister of 57
59	III 61	F	50	+++	-	-	+	++	-	-	0	Half sister of 60 and 64
60	III 63	F	45	+++	0	0	-	-	-	-	-	
61	IV 82	F	18	++	-	-	-	-	0	0	++	Daughter of 61
62	IV 83	F	15	++	-	-	-	-	0	+	+	Daughter of 61
63	III 64	F	50	+++	+	-	0	+	-	-	-	Sister of 61
64	IV 42	F	35	+++	+++	+++	++	+++	0	0	++	
65	IV 49	M	35	+++	+++	+++	+++	+++	0	0	+++	

\+ = Abnormal
++ = Markedly abnormal
+++ = Grossly abnormal
0 = No film available (radiograph)
\- = Normal.

affected family in pedigree I and the man is a member of Pedigree III. Children who were under 8 years were not examined radiologically. Of the 26 children who on radiological examination showed no abnormality, 24 were approximately 8 years or more and may remain normal or develop mild degrees of dysplasia while 2 were under 8 years of age and might still develop marked epiphyseal abnormalities at a later date. Few complete family units, consisting of both parents and all their offspring were examined. Of 45 matings, excluding the couples in generation I, both husband and wife were available for radiographs in only 17 cases (See Table XXII). For these 17 pairs, in 3 cases all the offspring were under 8 years and not examined. One such family was that of the dwarf proposi-tus III(53). In 5 units, one or more of the children were under 8 years, and in 4 units at least one of the offspring was working away from the area. So that, out of a total of 46 children, 30 were examined, 12 were under 8 years, and 4 were away. Only 6 complete family units with a total of 12 children were examined. The radiological findings are summarised in Table XXIII and only selected people will be discussed.

The persons III(29) and IV(38) are interesting in that they have an atypical form of the disease. Both, 111(29) and IV(38) as can be seen from Table XXIII, have evidence of dysplasia only in the ankles and the feet while the hips, hand, knees and spine are normal.

Also of interest are the man, III(10) who has short metatarsals and the typical deformities of the tarsal bones but no other abnormalities. His wife, III(11) is radiologically normal yet they have a 22 year old son with marked generalised epiphyseal dysplasia.

Patients IV(23) and (24) are 16 year old girl twins, both affected and have 9 year old twin sisters in whom no abnormality was detected radiologically. It is not known whether they are monozygous or dizygous. Such sets of twins should be studied in more detail as will be discussed later in this thesis.

In generation 2 it may be seen that of the 15 women who married the three brothers, II(4), II(11) and II(16), 13 were affected. Eleven of them produced one or more affected children. The two unaffected women produced five children of whom only one, a 9 year old was examined and was normal. The others were said to be normal.

The general findings in this pedigree may be summarised thus:

1. No information is available about the first generation.
2. There is vertical transmission of the disease through at least three generations of numerous family units.
3. There are no affected children with two normal parents.
4. Male and female siblings are both affected.
5. Of 61 descendants of generations II and III, 37 were examined radiologically. Seventeen were male and 44 female. Of these 8 males (47%) and 29 females (65%) were affected. Thus, about half the males and almost two-thirds of the females that were examined are affected. This is far higher than in the general population.

FIGURE 46

GENEALOGY II: THE NGUBANE FAMILY

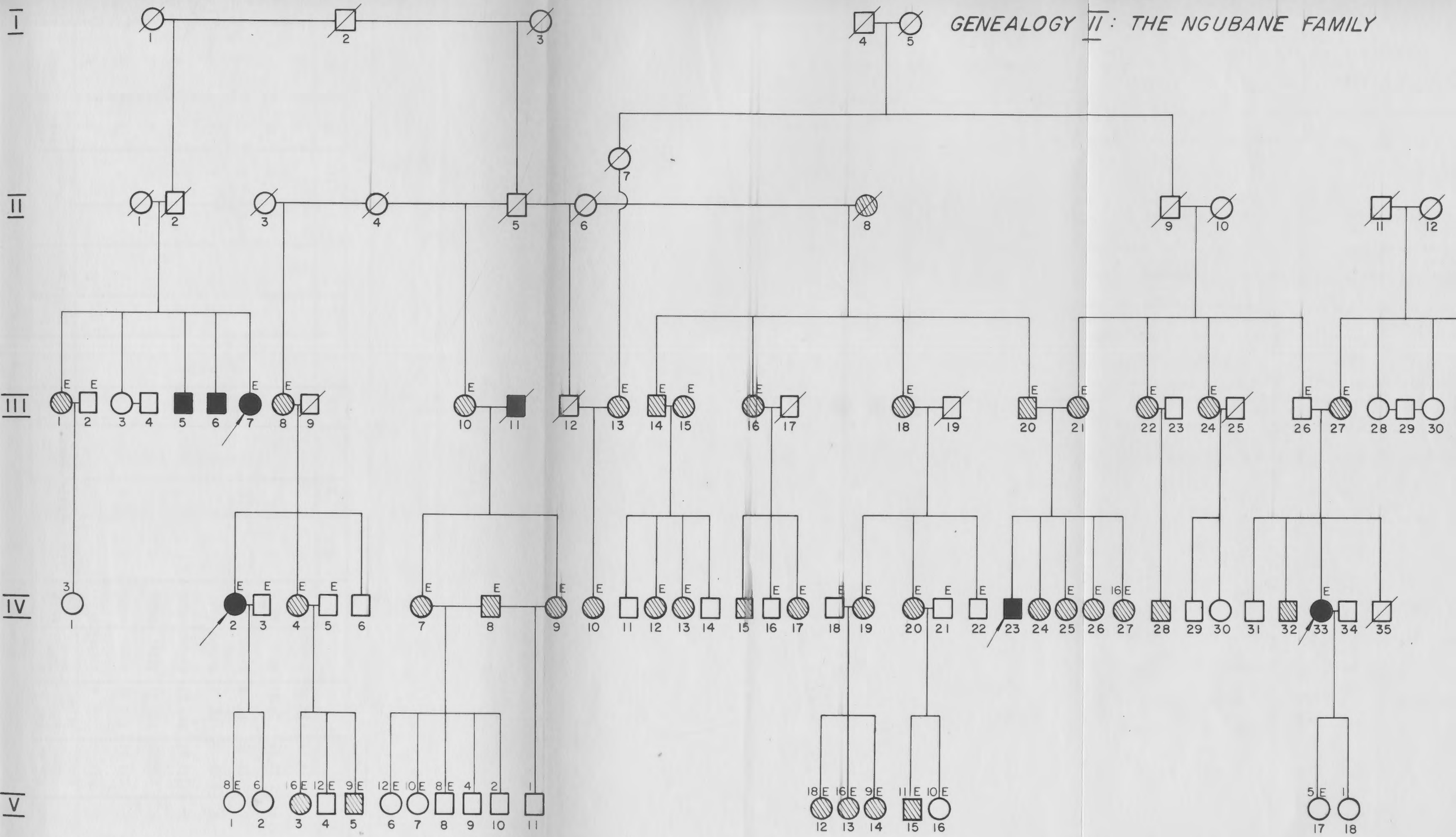


TABLE XXIV : ANALYSIS OF FAMILY UNITS FROM GENEALOGY 2

	Parents				Children											
	Identification		Disease status		Not examined radiologically					Examined radiologically						
Family unit	No. of husband.	No. of wife	Husband	Wife	8 years less	Male	Female	Male	Female	Male	Female	Male	Female		Total examined	Total
1	III 2	III 1	Normal	Afft.	1										0	1
2	III 14	III 15	Afft.	Afft.	0	2							2		2	4
3	III 20	III 21	Afft.	Afft.	0				1			1	3		4	5
4	III 26	III 27	Normal	Afft.	0	1		1					1		1	3
5	IV 3	IV 2	Normal	Afft.	1								1		1	2
6	IV 5	IV 4	Normal	Afft.						1		1	1		3	3
7	IV 18	IV 19	Normal	Afft.	0								3		3	3
8	IV 21	IV 20	Normal	Afft.							1	1			2	2
			Total:		3	3		1	1	1	1	3	11		16	23

TABLE XXV : AFFECTED PEOPLE FROM GENEALOGY 2 SHOWING DEGREE OF ABNORMALITY IN EACH JOINT ON RADIOLOGICAL EXAMINATION
(arranged by family unit)

No	Patient no.	Sex	Approx. age	Hips	Knees	Ankles	Feet	Hand	Elbow	Shoulders	Spine	Relationship
1	III 1	F	38	+++	+	+	0	-	-	-	-	
2	III 7	F	20	+++	+++	+++	+	++	-	-	++	Sister of 1
3	III 8	F	60	+++	+++	+	0	++	+	-	-	
4	IV 2	F	30	+++	++	++	+	+++	0	0	+	Daughter of 3
5	IV 4	F	35	++	-	+++	+	-	+	-	-	Daughter of 3
6	V 3	F	15	-	-	-	-	-	-	-	+++	Daughter of 5
7	V 5	M	9	+	-	-	-	-	-	-	-	Son of 5
8	III 10	F	65	+++	++	0	0	+++	0	0	0	
9	IV 7	M	50	+	-	-	-	-	0	0	-	Daughter of 8
10	IV 8	F	40	++	+	+	0	+	+	-	++	Husband of 9 and 11
11	IV 9	F	40	++	+	+	0	+	+	-	++	Daughter of 8
12	III 13	F	52	+++	++	+++	++	+++	+++	+	0	
13	IV 10	F	18	++	+	+	0	++	-	-	++	Daughter of 12
14	III 14	M	70	-	-	+	++	+	0	0	++	
15	III 15	F	65	++	+	+	++	+++	+++	+	-	Wife of 14
16	IV 12	F	28	+++	+	+	0	-	-	-	+++	(Daughters of 14 and 15)
17	IV 13	F	21	+++	+	+	++	++	-	-	+++	
18	III 16	F	60	+++	+++	0	0	+	0	0	0	
19	IV 17	F	25	+++	++	0	0	-	0	0	0	Daughter of 18
20	III 18	F	65	+++	++	0	0	+	0	0	0	
21	IV 19	F	45	+++	++	+	+	-	+	+	-	Daughter of 20
22	V 12	F	18	+++	+	-	0	++	-	-	++	Daughter of 21
23	V 13	F	16	+++	++	++	++	+++	-	-	++	Daughter of 21
24	III 20	M	60	+++	+++	++	+	+	-	0	++	
25	III 21	F	45	++	+	-	++	-	+++	-	-	Wife of 24
26	IV 23	M	20	+++	+++	+++	+++	+++	0	0	+++	Son of 24 and 25
27	IV 25	F	22	++	+++	+++	++	+++	0	0	++	Daughter of 24 and 25
28	IV 26	F	23	+	+	+	0	-	0	0	+	Daughter of 24 and 25
29	IV 27	F	16	++	-	+	0	-	0	0	-	Daughter of 24 and 25

(Continue on next page)

TABLE XXV (Continued)

No	Patient no.	Sex	Approx. Age.	Hips	Knees	Ankles	Feet	Hand	Elbow	Shoulders	Spine	Relationship
30	III 22	F	50	+++	+++	-	+++	+++	-	+++	+++	
31	III 24	F	55	+++	++	+	0	+	+++	+	-	Sister of 30
32	III 27	F	50	+++	+	++	0	+++	0	0	0	
33	IV 33	F	25	+++	+++	+++	++	+++	+	+	+++	Daughter of 32
34	IV 20	F	40	++	+	-	0	++	-	-	++	
35	V 15	M	11	++	++	++	+	-	+	+	++	Son of 34

GENEALOGY II : THE NGUBANE FAMILY (Fig. 46)

Investigations into this genealogy were commenced when the pedigrees of four independently ascertained dwarf probands were being compiled. These probands were persons II(7) and IV(2), IV(23) and IV(33).

It was found that IV(23) and IV(33) were first cousins, that III(7) and the mother of IV(2) were half first cousins, and that the mother of case IV(2) and the father of case IV(23),(III(8) and III(20), respectively, were half sibs, sharing a common father II(5) but born to different mothers.

This family aroused further interest, as one of the few instances of contravention of the taboo against marriage of two people with the same isibongo was found in this pedigree. (III(20) and III(21) were of the same clan name). On questioning them, no apparent relationship between the two families could be found as far back as the paternal grandfathers.

There were also numerous instances of marriage of women to a man of the same isibongo as her maternal grandfather. Although according to Bryant[27,28] this was forbidden, it appears fairly common practice now.

All 5 members of generation I and all 12 members of generation II are dead. Person II(8) is the only one definitely known to have been affected while conflicting reports have been made about the others.

In generation II the husbands of III(8), III(10), III(13), III(16), III(18) and III(24) were dead. Of these, one was said to be dwarfed,

and the disease status of the other five is unsure.

One of the probands, IV(23) left the area to work in Durban and was not radiologically examined. Of the 3 dwarfs who have been examined radiologically, III(7) and IV(23) have no offspring. IV(2) and IV(33), have children aged 8 and 6 years, and 5 and 1 years, respectively. Of the children aged 6 and 5, radiological examination of their joints revealed no abnormality, but only follow-up radiographs over at least 5 years will determine whether they are completely unaffected. The hip joint of the 8 year old, revealed very slight irregularity but follow-up examination is needed to distinguish whether she is affected or whether the apparent abnormality is only a normal developmental appearance.

There were 10 family units in this genealogy in which both husband and wife were examined radiologically, In Table XXIV, the family units are analysed. Again it can be seen that only in three cases, family units 6, 7 and 8 was the entire family available for examination. IV(7), IV(8) and IV(9) are the same people as III(41), III(42) and III(43) in Genealogy I and are not listed in Table XXIV.

IV(5) is unusual in that the only abnormality noted on examination of his joints was bilateral shortening of the 1st metacarpal bones while III(14) has osteoarthrosis of the ankles, metatarsal-phalangeal joints, and of the spine but normal hips and knees.

Again there is vertical transmission of the disease through at least three generations and in some cases 4 generations. Male and female

affected siblings are also noted. From generation III onwards the appearance of this pedigree is compatible with an autosomal dominant inheritance but even when allowance is made for the problems of obtaining accurate genealogical information, the apparent absence of the disease in all but one of the members of generations I and II must be considered.

FIGURE 47

GENEALOGY III : THE MDLETSHE AND MANUKUZA FAMILIES

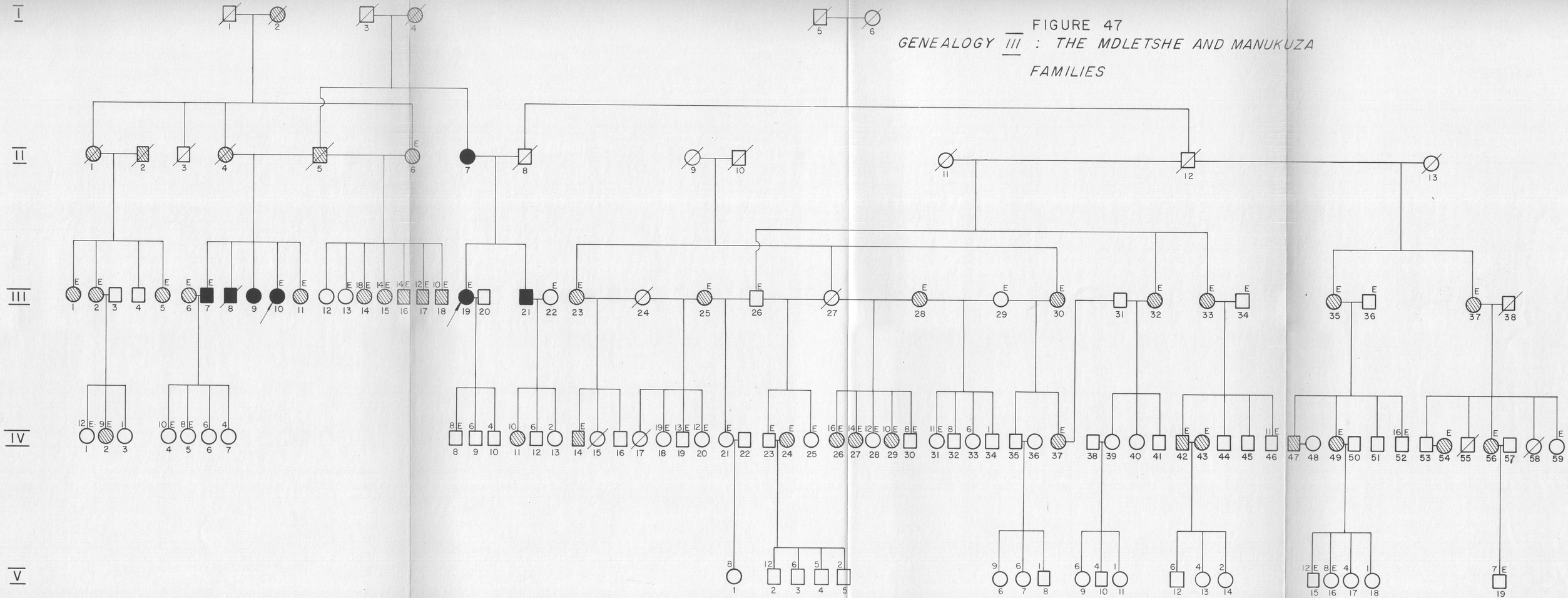


TABLE XXVI : ANALYSIS OF FAMILY UNITS FROM GENEALOGY 3

Parents					Children										
Identification			Disease status		Not examined radiologically					Examined radiologically					
	No. of husband	No.of wife.	Husband	Wife	8 years or less	Away-unsure Male	Away-unsure Female	Affected on history Male	Affected on history Female	Normal Male	Normal Female	Affected Male	Affected Female	Total Examined	Total
1	III 26	III 23	Norm	Afft		1						1		1	2
2	III 26	III 25	Norm	Afft							1			1	1
3	III 26	III 29	Norm	Norm	2					1	1			2	4
4	III 26	III 30	Norm	Afft		1							1	1	2
5	III 34	III 33	Norm	Afft		2				1		1		2	4
6	III 36	III 35	Norm	Afft		1		1		1			1	2	4
7	IV 23	IV 24	Norm	Afft	1									0	1
8	IV 42	IV 43	Afft	Afft	2	1								0	3
Totals:					5	6	0	1	0	3	2	2	2	9	21

TABLE XXVII : AFFECTED PEOPLE FROM GENEALOGY 3 (ARRANGED BY FAMILY UNITS) SHOWING DEGREE OF ABNORMALITY IN EACH JOINT ON RADIOLOGICAL EXAMINATION

No.	Patient No.	Sex	Approx. age	Hips	Knees	Ankles	Feet	Hands	Elbows	Shoulder	Spine	Relationship
1	II 6	F	40	+++	-	+	0	+	0	0	+	
2	III 14	F	18	+++	+++	+++	+++	+++	0	0	++	Daughter of 1
3	III 15	F	16	+++	+++	+++	+++	+++	0	0	++	Daughter of 1
4	III 16	M	14	+++	+++	+++	+++	+++	0	0	+++	Son of 1
5	III 17	M	12	+++	+++	+++	+++	-	0	0	+++	Son of 1
6	III 18	M	10	+++	+++	+++	+++	-	0	0	-	Son of 1
7	II 7	F	50	+++	+++	++	+	++	+++	++	++	
8	III 19	F	28	+++	+++	+++	+++	+++	+++	+++	+++	Daughter of 7
9	III 1	F	40	+++	++	+	0	0	0	0	+	
10	III 2	F	35	+++	+	+++	0	0	0	0	+	Sister of 9
11	IV 2	F	9	+	-	-	-	0	0	0	0	Daughter of 10
12	III 5	F	30	+++	+	-	0	+	0	0	0	Sister of 8 & 10
13	III 6	F	25	+++	+++	+++	+++	+++	+++	+++	+++	
14	III 7	M	30	+++	+++	+++	+++	+++	+++	+++	+++	Husband of 13
15	III 10	F	25	+++	+++	+++	0	+++	0	0	+++	Sister of 14 & 16
16	III 11	F	22	++	++	++	0	-	0	0	0	Sister of 14 & 15
17	III 23	F	55	+++	+++	++	++	0	+++	+	-	
18	IV 14	M	30	+++	+	+	++	-	0	0	-	Son of 17
19	III 25	F	55	++	+	+	+	-	+	+	-	
20	III 28	F	40	+++	++	++	+	+++	+	0	++	
21	IV 26	F	16	++	+	+	0	-	0	0	++	Daughter of 20
22	IV 27	F	14	++	+	+	0	-	+	-	-	Daughter of 20
23	IV 29	F	10	++	-	+	0	-	0	0	+	Daughter of 20
24	III 30	F	65	+++	-	-	-	-	-	-	-	
25	IV 37	F	40	+++	++	0	0	0	+	0	0	Daughter of 24
26	III 32	F	65	+++	++	0	0	+	0	0	0	
27	IV 39	F	40	-	-	-	-	-	-	-	-	Daughter of 26
28	III 33	F	55	+++	++	0	0	++	0	0	0	
29	IV 42	M	30	+++	-	-	0	-	0	0	0	Son of 28
30	III 35	F	60	+++	+	++	0	++	0	0	0	
31	IV 49	F	35	+++	+++	0	0	-	0	0	0	Daughter of 30
32	III 37	F	50	++	+	0	0	++	0	0	0	
33	IV 56	F	30	+++	+	++	0	++	0	0	0	Daughter of 32
34	IV 11	F		+	++	+	0	-	0	0	0	
35	IV 24	F	40	+++	++	-	0	+++	-	-	+	
36	IV 43	F	30	++	++	+	0	+	0	0	0	
37	IV 54	F	20	++	-	-	0	+	0	0	-	
38	III 26	M	60	-	-	-	*'	-	-	-	-	

*' Bilateral short 1st metacarpals.

GENEALOGY III : THE MDLETSHE CLAN (Fig. 47)

This genealogy was compiled during the tracing of the families of two independently ascertained dwarfed probands, III(10) and III(19), and during investigation into the family of the third proband III(10), who was the youngest affected person found during the pilot clinical survey. It is also of interest as an example of polygamy, which is common in the Mseleni area, particularly because the man concerned III(26) and 5 of his 7 wives, were available for radiological examinations.

Three of the dwarfs have children, but of the total of 10 children, only 2 are over 8 and they are both only 10. The one, IV(11) shows definite signs of MJD, but IV(4) appears to be normal.

Of 22 possible mating pairs in only 9 cases were both husband and wife available for examination, and in 5 of these cases, the husband was the same man III(26),(Table XXVI).

Details of 5 generations of this family could be recorded but again the accuracy of information regarding the MJD status of the deceased ancestors is uncertain. It is probably fair to assume that if an individual is said to have been affected that he or she probably was, but if he is said to be unaffected there may have been radiological evidence of the disease.

This pedigree appears to be compatible with a simple autosomal inheritance but for the apparent absence of disease in II(11) and II(13), both of whom are the mothers of two affected daughters. Again, since both

these women are dead it is not known whether they had radiological stigmata of the disease. There is vertical transmission of the disease through 3 to 4 generations, and both male and female sibs are affected.

FIGURE 48

GENEALOGY IV: THE SIBIYA / NXUMALO FAMILY

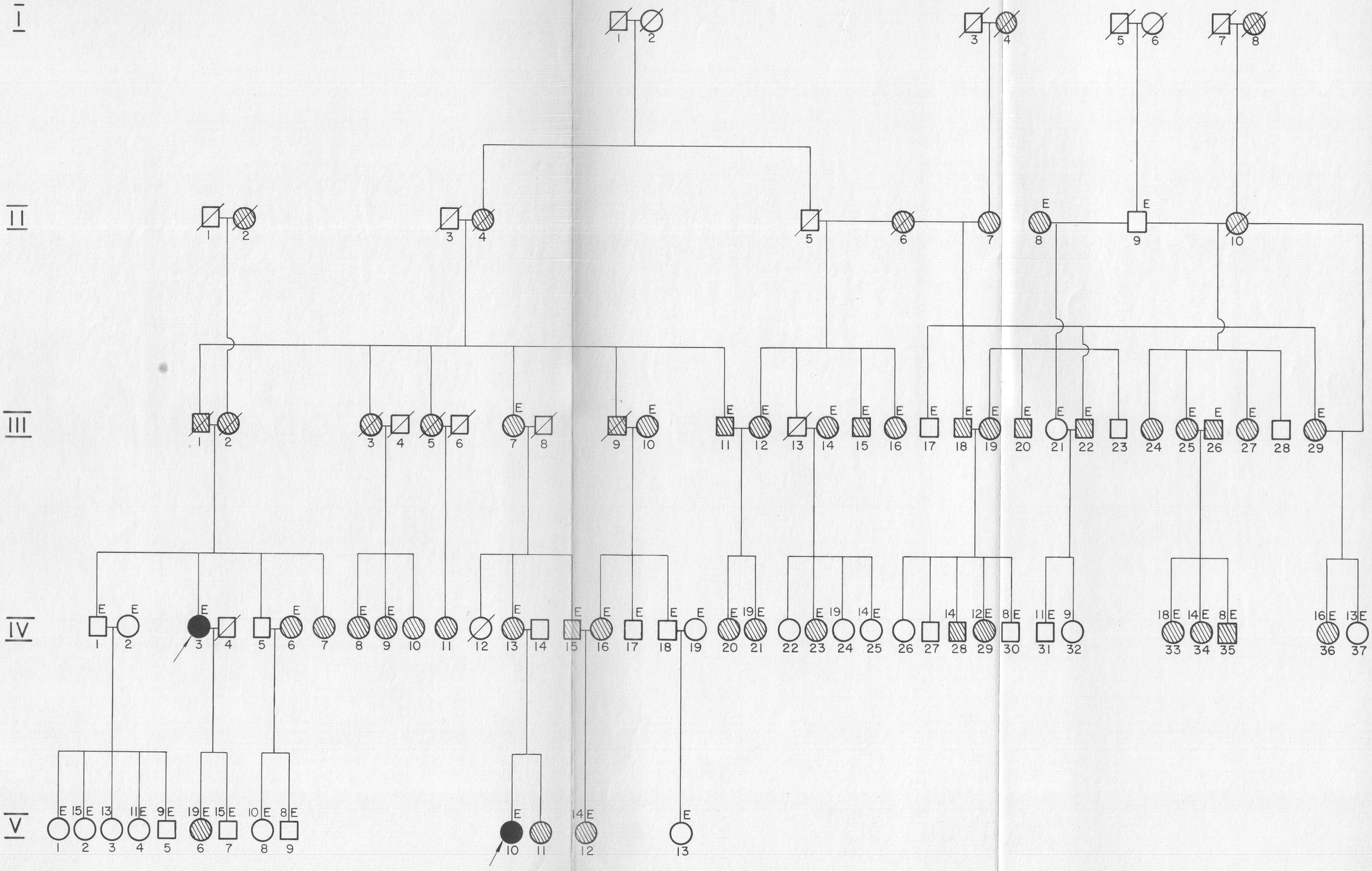


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TABLE XXVIII : ANALYSIS OF FAMILY UNITS FROM GENEALOGY 4

No.	No of Husband	No of wife	Husband	Wife	8 years or less	Away unsure Male	Away unsure Female	Affected on history Male	Affected on history Female	Normal Male	Normal Female	Affected Male	Affected Female	Total examined	Total
1	II 9	II 8	Norm	Afft	0	1					1	1	1	3	4
2	II 9	III 29	Norm	Afft	0						1		1	2	2
3	III 11	III 12	Afft	Afft	0								2	2	2
4	III 18	III 19	Afft	Afft	1	1	1					1	1	2	5
5	III 22	III 21	Afft	Norm	0					1*	1			2	2
6	III 26	III 25	Afft	Afft	0							1	2	3	3
7	IV 1	IV 2	Norm	Norm	0		1			1	3			4	5
8	IV 15	IV 16	Afft	Afft	0								1	1	1
9	IV 18	IV 19	Norm	Norm	0						1			1	1
				Total:	1	2	2	0	0	2	7	2	8	20	25

* Bilateral lunato-triquetral fusion but no other evidence of abnormality.

TABLE XXIX : AFFECTED PEOPLE FROM GENEALOGY 4 (ARRANGED BY FAMILY UNITS) SHOWING DEGREE OF ABNORMALITY IN EACH JOINT PRESENT ON RADIOLOGICAL EXAMINATION

No.	Patient No.	Sex	Age	Hips	Knees	Ankles	Feet	Hand	Elbow	Shoulder	Spine	Relationship
1	II 8	F	65	+++	+++	++	+	+++	+++	0	-	
2	III 20	M	40	+++	++	+	+++	+++	+	-	+++	Son of 1
3	III 19	F	45	+++	-	+	-	-	0	0	-	Daughter of 1
4	III 18	M	50	+++	-	+	-	-	++	-	-	Husband of 3
5	IV 29	F	12	+++	+++	+++	++	+++	0	0	++	Daughter of 4&3
6	III 22	M	40	+++	++	+	++	-	0	-	+++	Brother of 4
7	III 7	F	65	+++	++	+++	+	+	++	++	-	
8	IV 13	F	40	+	+	-	+	++	0	+	-	Daughter of 7
9	IV 10	F	20	+++	+++	+	+	-	0	0	+	Daughter of 8
10	IV 15	M	50	+	-	-	+	+	0	0	-	Son of 7
11	IV 16	F	45	+++	-	-	0	-	-	-	-	Wife of 9
12	IV 12	F	16	+++	++	++	+	-	0	0	++	Daughter of 7&9
13	III 10	F	60	+	-	-	-	-	0	0	+	Mother of 10 & 13. Sister of7
14	III 11	M	50	+++	+++	+++	+++	+++	0	0	+	
15	III 12	F	45	+++	+++	+	+++	+++	0	0	++	Wife of 14
16	IV 20	F	24	+++	++	-	+	+++	0	0	++	Daughter of 14 and 15
17	IV 21	F	19	+++	+	+	-	-	0	0	++	ditto
18	III 14	F	45	+	-	-	-	-	-	-	-	
19	IV 23	F	23	++	-	-	-	-	-	-	-	Daughter of 18
20	III 15	M	40	+++	++	+++	+	++	0	0	+	
21	III 16	F	35	+++	-	-	+	++	0	0	+	Sister of 20
22	III 25	F	35	+++	++	-	0	-	-	-	+++	
23	III 26	M	40									Husband of 22
24	IV 33	F	18	+	-	-	0	-	-	-	+++	Daughter of 22
25	IV 34	F	14	+	++	+	-	++	-	-	+++	Daughter of 22
26	IV 35	M	8	+++	++	++	+++	+	0	0	++	Son of 22 & 23
27	III 27	F	35	+++	+	-	-	++	-	-	-	Sister of 22
28	III 29	F	36	+++	++	++	++	+	0	0	0	
29	IV 36	F	16	+	+	+	+	+	0	0	+	Daughter of 28

GENEALOGY IV : THE SIBAYA - NXUMALO FAMILIES (Fig. 48)

The probands for this genealogy were the two independently ascertained dwarfed individuals IV(3) and V(10) who were later found to be second cousins. Further examples of first cousin marriage are seen in this pedigree in the 3rd and 4th generation.

The MJD status of generation I was uncertain with the exception of I(4) and I(8), who were said to have been definitely affected. Affected people can be traced through four generations in several family lines. There were 8 family units in which both parents were examined. In two cases both parents were normal. In the one pair, the normal husband was descended from two affected parents, yet none of his five offspring were affected. The other pair had only one child, also normal. (Table XXVIII).

The older dwarfed woman has 2 children of which the daughter is affected, and the son normal. The younger has no children.

This disease pattern in this pedigree appears to be compatible with that of an autosomal dominant gene with high penetrance.

FIGURE 49

GENEALOGY V: THE GUMEDE / MTHEMBU FAMILY

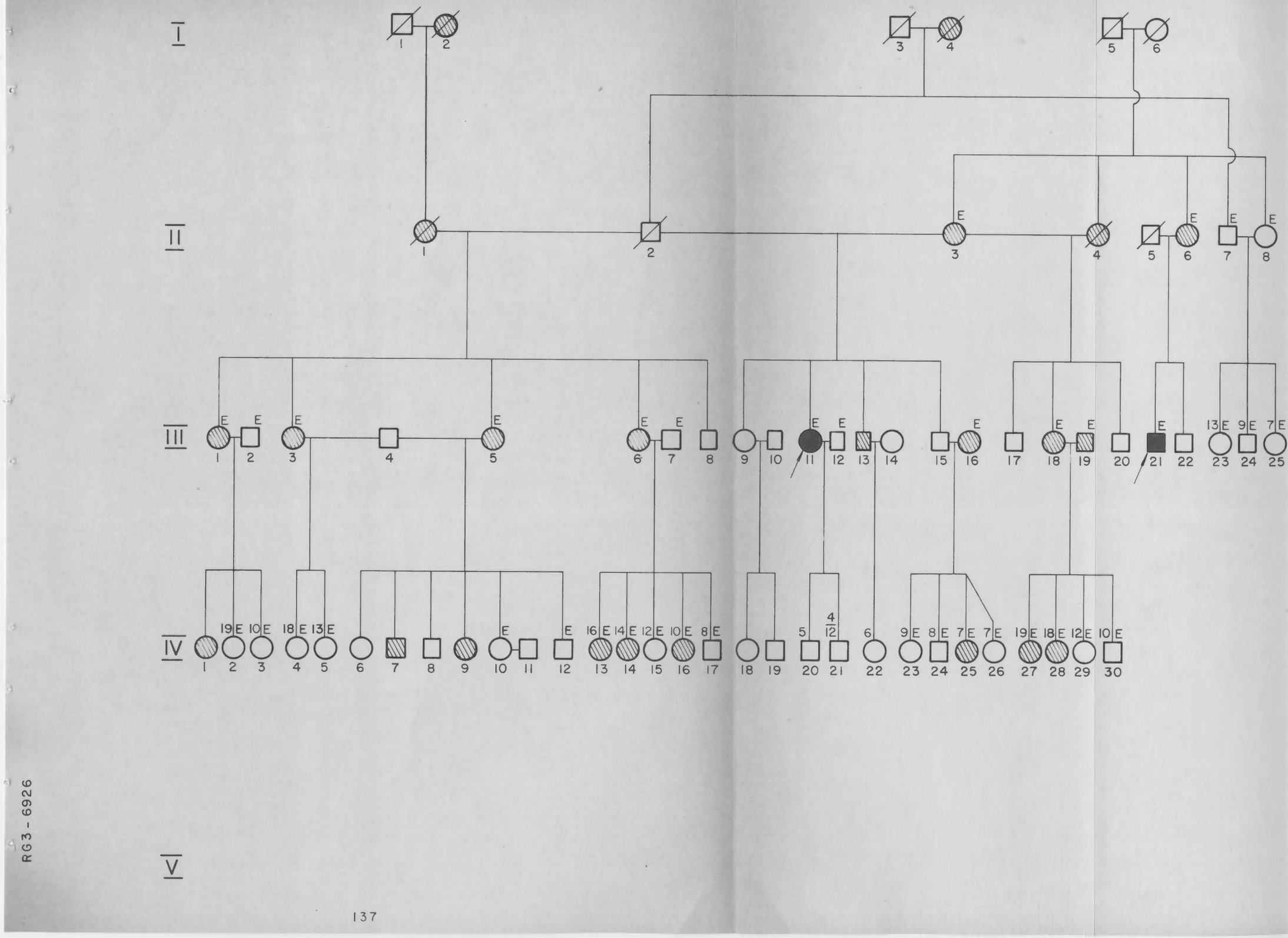


TABLE XXV : ANALYSIS OF FAMILY UNITS FROM GENEALOGY 5

	Parents				Children											
	Identification		Disease status.		Not examined radiologically					Examined radiologically						
Family unit	No. of husband.	No. of wife	Husband	Wife	8 years or less	Away-unsure Male	Away-unsure Female	Affected on history Male	Affected on history Female	Normal Male	Normal Female	Affected Male	Affected Female	Total examined	Total
1	II 7	II 8	Normal	Normal	1					1	1			2	3
2	III 2	III 1	Normal	Afft.	0				1		2			2	3
3	III 7	III 6	Normal	Afft.	0					1	1		3	5	5
4	III 12	III 1	Normal	Dwarf	2									0	2
5	III 19	III 18	Afft.	Afft.	0					1	1		2	4	4
				Total:	3				1	3	5		5	13	17

TABLE XXXI : AFFECTED PEOPLE FROM GENEALOGY 5 (ARRANGED BY FAMILY UNIT) SHOWING DEGREE OF ABNORMALITY IN EACH JOINT ON RADIOLOGICAL EXAMINATION

No.	Patient No	Sex	Age	Hips	Knees	Ankles	Feet	Hand	Elbow	Shoulder	Spine	Relationship
1	III 3	F	60	+++	0	0	0	+++	0	0	0	
2	III 11	F	30	+++	+++	+++	0	+++	0	0	0	Daughter of 1
3	II 6	F	50	+++	++	++	0	+++	0	0	-	
4	III 21	M	25	+++	+++	+++	+++	+++	0	0	+++	Son of 3
5	III 1	F	50	+++	++	+	0	++	0	0	+	
6	III 3	F	40	+	+	-	-	-	-	-	-	
7	III 5	F	45	++	+	-	+	++	+	-	-	Sister of 6
8	III 6	F	35	+++	++	+	+	+++	+	0	++	Sister of 7 & 8
9	IV 13	F	16	++	-	-	0	-	0	0	0	Daughter of 8
10	IV 14	F	14	++	+	-	0	-	0	0	0	Daughter of 8
11	IV 16	F	10	++	-	-	0	-	0	0	0	Daughter of 8
12	III 16	F	30	+++	+	-	0	+	-	-	++	
13	IV 25	F	7	++	+	+	+	-	0	0	-	Daughter of 12
14	III 18	F	40	+++	+	+	+	++	+	-	-	
15	III 19	M	45	-	-	-	+	+	0	0	++	Husband of 14
16	IV 27	F	19	+	-	++	+	-	0	0	+	Daughter of 14 & 15
17	IV 28	F	18	+	-	-	-	-	0	0	+	ditto
18	IV 29	F	12	-	-	-	+	+	0	0	+	ditto

\+ = Abnormal
++ = Markedly abnormal
+++ = Grossly abnormal

0 = No film available
\- = Normal

GENEALOGY V : THE GUMEDE MTHEMBU CLANS

This genealogy shows the descendants of two brothers II(2) and II(7) who married respectively 3 sisters and 1 sister from a single family. II(7) was clinically and radiologically normal and II(2) (deceased) is reported to have been normal. Two dwarfs, III(11) and III(21), who are first cousins, were independently ascertained probands for this family. Neither have offspring over 10 years of age.

Since this is a relatively small pedigree of only 59 living members only 5 radiologically examined mating pairs were obtained. They had a total of 17 children of whom 2 were under 6 years, and 1 was pregnant and therefore not fully examined. It may be seen that two of the people marrying into the family were affected.

The analysis of the disease status of the family units is shown in Table XXX . It can be seen that the normal couple had 3 normal children. Since II(2) was reportedly normal, it is probable that his daughters III (1), and III(6) in family units 2 and 3 were heterozygotes. Under an autosomal dominant hypothesis this would imply that half of their offspring would be affected if married to unaffected males as they are. In fact, of the 3 children of III(1), 1 was affected and of the 5 children of III(6), 3 were affected. Family unit 5, consists of 2 affected people. His wife, also a child of II(2) is probably heterozygote. The husband too had an affected mother and a reportedly normal father, and would probably be heterozygous. Three of their 4 children were affected.

Two individuals are of interest. The 12 year old girl IV(28) and her father III(19), both have radiologically normal hips, knee and ankle joints. The father has a deformed navicular bone in the foot, with bilaterally deformed ulnae, and anterior lipping of the lumbar vertebrae. The daughter has deformed navicular bones, fusion of the hamate and capitate in the right hand and step-like defects in the lumbar vertebrae. While the carpal fusion may be a coincidental finding, the navicular abnormalities are typical of those seen in the Mseleni Joint Disease sufferers. These people the author considered to be affected but with a low degree of expressivity, i.e. as in the group called "atypical" in Section II.4.3.

This pedigree too is not incompatible with an autosomal dominant inheritance.

DISCUSSION OF THE GENEALOGICAL STUDIES

Identification of a founder group of ancestors

Accurate genealogical data was obtained in most instances for two generations of progenitors of the adults interviewed. Frequently, however, the respondents could not state whether a grandparent had been affected and on several occasions there were conflicting opinions concerning a single individual.

Several subjects could not remember the names of their maternal or paternal grandparents, and great grandparents were almost never remembered. For these reasons a founder group of ancestors could not be traced for this population.

Affected members in generations I and II

The disease status of deceased members of generation I and sometimes generation II as indicated in the genealogies is not accurate with regard to members marked as "unaffected". It is possible that some may have had MJD but the author has chosen to err on the side of caution. It seems reasonable to assume that where a subject was said to have been affected, he or she probably had the condition though one or two "old age" osteoarthritis sufferers may thus be wrongly included.

It is not known therefore whether the apparent onset of MJD for the first time as for example in generation III of Genealogy 2 is a genuine phenomenon or a result of this problem of ascertainment. Similarly there are several instances where elderly affected subjects state

that their deceased parents were normal. An example is in Genealogy 3. Here the subjects III(32)and III(33) stated that they thought the two wives of II(12) , their mother, II (11) and stepmother II(13), had been unaffected while they themselves definitely had MJD.

If correct, this would be a pointer towards an environmental cause with the disease appearing for the first time in four of the fice children of an unaffected man and his two unaffected wives and thereafter maintaining a pattern similar to that of the dominant gene with high penetrance. It is highly unlikely that mutation to a dominant gene could act in this fashion. Unfortunately, it is doubtful whether this type of problem can be resolved because of the obvious difficulties encountered when studying an unsophisticated population as in Mseleni.

Marriage patterns

1. Consanguinity was not a prominant feature as there were only three instances in these pedigrees. First cousin marriages were in fact disfavoured.
2. Polygamy was encountered frequently, several of the men having as many as seven wives. However, it can be seen from the younger generations that this practice is decreasing.
3. Mating was non-random as brothers and sisters from a family preferentially married sisters and brothers from another family. There were numerous instances where a man would be married to at least three or more sisters or half-sisters from another family. However, since the two families were unrelated this does not imply consanguinity.

PATTERN OF DISEASE OCCURRENCE

Within each pedigree vertical transmission of the disease through 3 or 4 generations to both male and female descendants is a prominent feature. This is very strongly suggestive of an autosomal dominant gene with high penetrance.

It was frequently noted that several wives in a kraal were affected. This, together with the peak age of onset of symptoms of 30-40 years, or after 2 or more babies, could suggest a horizontal transmission of the disease among members of a single generation. However, it is obvious that with a prevalence rate of 46% (radiological study) among adult women, almost half the wives in any one family should be affected.

The question to be considered is whether the joint pathology, usually osteoarthrosis, developed de novo after a time of living in that kraal, or whether at the time of marriage into the kraal the woman already had asymptomatic epiphyseal dysplasia which with increase in age, the stresses of childbearing and of working in the fields, developed into a severe osteoarthrosis producing the symptoms of joint pain. While the former situation would clearly represent a horizontal transmission of the disease implicating an environmental agent, the latter situation would obviously produce a spurious fascimile. This is an extremely important point which remains to be investigated.

At least one instance of male to male transmission was noted, in Genealogy 1.

SEGREGATION FREQUENCIES

In order to decide whether the segregation frequencies for the various types of matings conformed to the Mendelian form of inheritance, proposed in the hypothesis, i.e. simple autosomal dominant, family units were analysed. Since radiologically there was no indication as to whether a sufferer was homozygous or heterozygous, it was decided that two phenotypes would be used to indicate each person's status with regard to MJD, namely, normal or affected.

Characteristics expected for a dominant condition

If a dominant gene is responsible for MJD, we would expect to find (if complete penetrance is assumed):

(a) Vertical transmission of the disease

(i) an affected child must have at least one affected parent;

(ii) two normal parents cannot produce an affected child.

(b) Minimum number of affected offspring

If one parent is affected, at least 50% of the offspring should be affected.on average.

Effect of sex of offspring on genotype and phenotype frequencies

In view of the higher percentage of affected people among women, the possibility of X-linked dominance was raised. The percentage of the different genotypes and phenotypes expected under a system of autosomal dominance and of X-linked dominance are seen in Tables XXXII and XXXIII respectively. It can be seen that in the auto-

TABLE XXXII : PERCENTAGE OF EACH GENOTYPE EXPECTED FOR ALL POSSIBLE MATING TYPES IN AN AUTOSOMAL DOMINANT CONDITION

			Affected MM	Affected mm	Normal mm	Total
1.	Affected and Normal					
	Mm	& mm	50	50		100
	MM	& mm	100			
2.	Affected & Affected		25	50	25	100
	Mm	& Mm	50	50		100
	Mm	& MM	50	50		100
	MM	& MM	100			100
3.	Normal & Normal					
	mm	& mm			100	100

TABLE XXXIII : PERCENTAGE OF EACH GENOTYPE EXPECTED FOR ALL POSSIBLE MATING TYPES IN AN X-LINKED DOMINANT CONDITION

Mating type			Phenotype	Affected female		Normal Female	Affected male	Normal male	Total.
			Genotype	X^mX	X^mX^m	XX	X^mY	XY	
1. Affected female X normal male.									
(a)	X^mX	X	XY	25		25	25	25	100
(b)	X^mX^m	X	XY	50			50		100
2. Affected female X Affected male.									
(a)	X^mX	X	X^mY	25	25		25	25	100
(b)	X^mX^m	X	X^mY		50		50		100
3. Normal female X Affected male.									
	XX	X	X^mY	50				50	100

Note: 1. No male to male transmission

2. All daughters of an affected male will be affected.

somal dominant condition, although the percentage of affected and normal children varies with each type of mating, the sex of the children is of no significance. Similarly, in the mating of affected female and normal males under the condition of X-linked dominance, males and females have an equal chance of being affected or normal.

However, in the X-linked dominant condition, where the male partners is affected, a sex ratio of affected children will exist: i.e. in mating 2a (Table XXXIII) there will be 2 affected girls for 1 affected boy, and in mating type 3 (Table XXXIII) all the girls will be affected and all the boys normal.

Specific features distinguishing the two types of dominance

Autosomal	X-linked dominant
Male and females equally affected.	No male to male transmission. All daughters of an affected male will be affected.

Results from the 5 genealogies combined

Both parents unaffected: There were 4 family units where both parents were radiologically unaffected. The number of children in each unit was 1, 2, 2 and 4. All nine were radiologically unaffected.

One or both parents affected: The ratio of affected sons to the total number of sons was determined for each individual family and an average calculated. The same calculation was performed for the daughters. The following results were obtained:

There were 13 males with one affected parent. The average ratio was 0,46 and the standard deviation 0,46.

There were 21 females with one affected parent. The average ratio was 0,45 and the standard deviation 0,45.

No significant difference ($P > 0,05$) was demonstrated between males and females.

There were 11 males with both parents affected. The average ratio was 0,59 and the standard deviation 0,47.

There were 20 females with both parents affected. The average ratio was 0,8 and the standard deviation 0,36.

Again, no significant difference ($P > 0,05$) was demonstrated between males and females.

Since no significant difference could be demonstrated for either of the averages between males and females, males and females were grouped together and the average ratio of affected to unaffected children for each mating type was calculated. These were 0,46 for the children of one affected parent (S.D. = 0,37) and for those of both affected parents 0,73 (S.D. = 0,36). These differ significantly, ($P < 0,05$).

It is apparent from this study that there is no difference between males and females in the proportion of affected children in a family. However, there is a difference in the proportions of affected children between the families when one or both parents are affected.

It must be noted that since the phenotype of the affected parent may correspond to more than one genotype (heterozygous or homozygous) these averages would not follow simple Mendelian ratios.

COULD THE DISORDER BE DUE TO A RECESSIVE GENE?

Assumptions that may commonly be made when dealing with a rare gene in a population, do not necessarily hold true in a population where approximately half the adult population claims to be dwarfed.

It is therefore possible that where the prevalence rate is so high, homozygous affected individuals may mate with heterozygous carriers and although the gene may be recessive in nature, a spurious or quasidominant pedigree may result. This possibility has also to be considered in the Mseleni population.

However, by considering the families with two affected patients, it is obvious that the Mseleni disorder, if genetic in origin, cannot be of a recessive type.

An affected person would be of the homozygous genotype MM. The offspring of a mating by two such persons would produce only homozygous affected offspring. In the 19 families with two affected parents there were 15 normal children. A recessive gene cannot therefore be responsible for MJD.

THE SIGNIFICANCE OF THE DWARFS

We have, however, not taken into account in discussing phenotypes the dwarfed people with MJD. There appear in fact to be 3 major phenotypes:

1. Normal people, unaffected by MJD;
2. Affected people with a wide variation in stature;

3. Dwarfed people which include the true dwarfs (130 cm or less as adult height) and the so-called "little people" (those with a mature height of 152,3 cm or less)[162].

The dwarfs could be explained in one of two ways:

(a) As the homozygous form of the disease;

(b) as a manifestation of greater expressivity.

In an attempt to resolve this question, a further study of 27 of the Mseleni dwarfs has been carried out, and is presented in the following section.

CONCLUSIONS FROM THE GENEALOGICAL STUDY

It is apparent that in a situation such as the Mseleni studies, where no historical records are available, where information on ancestry is only accurate for two generations back, where the disorder has a variable age of onset and where the absence of symptoms does not necessarily indicate absence of disease, a genealogical/radiological study at a fixed point in time can of necessity result in only a limited answer. Within these limitations however, a fair amount of data has emerged from this study. While there is no conclusive proof that MJD is an inherited disorder, nothing was found in these studies to contrdict the hypothesis of a dominant mode of inheritance. On the contrary, evidence in support of simple autosomal dominance was found.

1. The disorder has been traced through 3 to 4 generations in several families.
2. No significant difference was found in the proportion of male or female offspring who were affected.
3. A significant difference in the proportion of affected children was found between families where one parent was affected or where both were affected.
4. Within each family unit where at least one parent was affected, the numbers of affected children were compatible with a dominant gene of high penetrance.
5. In those family units where both parents were normal (confirmed radiologically) no affected children were found. This is particularly significant for the instance in Genealogy 4, where the normal hus-

band was descended from two affected parents, and had two affected sibs, yet none of his 5 children were affected.

6. An instance of male to male transmission (Genealogy 1) and the equal sex ratio exclude X-linked dominance, while the presence of normal children in the families with both parents affected excludes a recessive gene.

There are however problems which remain to be resolved.

These are:

1. The question of possible horizontal transmission of the disease among wives in a single kraal.
2. The apparent appearance of the disorder for the first time in several members of generation II in Genealogy 3.
3. The problem of whether a disorder could attain so high a prevalence in a population not completely isolated from other human contact.

This question of a possible founder affect is discussed in section III.2.7.

III.2.5 A STUDY OF THE MSELENI DWARFS

III.2.5 A STUDY OF THE MSELENI DWARFS

Objectives: A number of extremely stunted individuals were noticed by the author while visiting kraals in Mseleni and Manaba. The relationship of the dwarfism among the Mseleni population to the joint disease was of interest. The purpose of the dwarf studies was to determine whether the dwarfs represented a different entity to the Mseleni Joint Disease or whether they formed part of the MJD spectrum. If the latter applied, and a genetic aetiology was suspected, did they represent the homozygous form of the disease or merely a greater degree of expressivity.

Methods: For the purpose of this study, the criteria defined by Silverman[162] were adopted. He considered as "little people", those individuals with a mature height of 152.4 cm (60") or less. A "dwarf" was defined as an individual whose mature height is less than 132 cm (52").

During the renumeration of the population, the interviewer enquired at each kraal whether there were dwarfed individuals in the family. All the dwarfed people who were not out of the area or otherwise unavailable were then seen by the author, and where possible examined radiologically. Blood was taken for biochemical and chromosome studies from as many as possible. These dwarfs formed the probands for the genealogical studies.

Results: Forty dwarfed individuals who could be classified as "little people" were identified from the Mseleni and Manaba areas. These were all adults with the exception of 1 girl of 15 years. Of these 27 were seen and interviewed by the author. The data presented was obtained from

Fig. 50: A group of 'little people' contrasted with the two health assistants responsible for the fieldwork.

Fig. 51: Extreme *genu vulgum* is a fairly frequent finding

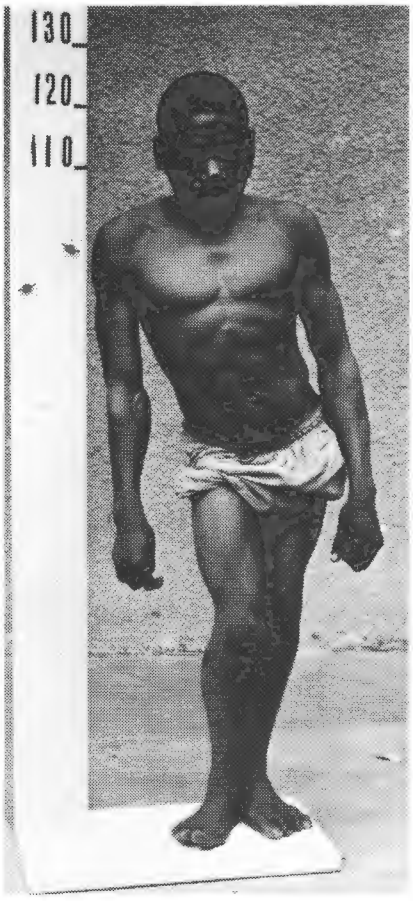


Fig. 52: Asymmetrical leg shortening.

Fig. 53: Characteristic stance of adult with Mseleni Joint Disease

GAcsir01HL2172*174

these subjects. (Ten of these dwarfs can be seen in Fig. 50 with the 2 fieldworkers responsible for the census.) Of the remaining 13, all 5 were males working outside the area and 1 refused to be examined. The other 8 were examined during the pilot clinical survey but were not available in the present study. These were females.

The 27 subjects were classified into 3 groups according to their height as in Table XXXVI Dwarfs were those people with an mature height of 132 cm or less; between 132 and 142 cm the subjects were regarded as being moderately dwarfed, while males between 142 and 152 cm were considered as short. Since the average height of the women with joint disease seen in the clinical survey was 152 cm, it was felt that a height of over 142 cm in the women bordered on the normal for the group and accordingly no woman over 142 cm in height was considered dwarfed for the purpose of this survey.

TABLE XXXVI CLASSIFICATION OF THE DWARFED INDIVIDUALS ACCORDING TO THEIR HEIGHT

Classification	Height	Subjects of study Male	Female	Total in survey	Seen in clinical survey females	Total
Dwarf	132 cm or less	4	11	15	4	19
Moderately dwarfed	133 - 142 cm	0	9	9	4	13
Short	143 - 152 cm	2	N/A	2	N/A	2
		6	20	26	8	34

Details of these 27 dwarfs are given in Table XXXVII.

TABLE XXXVII : DETAILS OF THE 27 DWARFED INDIVIDUALS

No.	Subject	Sex	Approx. age.	Genealogy	Case number	Height (cms)	Karyo-type	M.P.S. studies	Routine tests	Striking features
1	MN	M	25	-	-	117	46 XY	-	-	Asymmetrical leg length.
2	MM	F	20	-	-	118	46 XX	Yes	-	
3	DM	F	20	-	-	118	46 XX	Yes	-	
4	BM	F	25	III	III 19	119	-	Yes	Yes	Short stubby hands and toes
5	NN	F	25	II	IV 33	127	46 XX	Yes	-	Severe genu valgum
6	NM	F	25	-	-	127	-	Yes	Yes	
7	MT	F	50	-	-	127	46 XX	-	-	
8	NK	F	15	-	-	127	46 XX	Yes	Yes	Short trunk and neck
9	SZ	F	50	IV	IV 3	129	-	-	Yes	
10	NN	F	20	II	III 7	129	46 XX	Yes	-	Severe genu valgum
11	MM	M	30	1	III 53	129	46 XY	Yes	-	Leg shortening
12	GM	F	30	-	-	129	-	-	-	
13	CN	M	25	V	III 21	129	-	Yes	-	Asymmetrical leg length
14	GM	F	30	III	III 10	131	-	-	Yes	

TABLE XXXVII : (Continued)

No.	Subject	Sex	Approx. age.	Genealogy	Case number	Height (cms)	Karyo-type	M.P.S. studies	Routine tests	Striking features
15	VM	M	30	I	III 36	132	-	Yes	-	Overlapping toes and club feet
16	NS	F	30	V	III 11	133	-	Yes	-	
17	GM	F	50	III	II 7	134	-	Yes	Yes	Walks with 2 sticks
18	FM	F	30	-	-	134	-	Yes	Yes	Walks with 2 sticks
19	NM	F	25	-	-	136	-	-	-	
20	SG	F	35	-	-	140	-	Yes	Yes	Severe genu valgum
21	NS	F	30	II	IV 2	140	-	Yes	Yes	Severe genu valgum
22	PS	F	25	-	-	141	-	-	-	
23	LS	F	25	IV	-	142	-	-	-	
24	MM	F	25	1	III 58	142	-	Yes	-	
25	MM	M	30	-	-	148	-	-	Yes	
26	NM	M	30	-	-	151	-	-	-	Asymmetrical leg length
27	MM	M	35	III	III 7	Not recorded	-	-	-	

TABLE XXXVIII : FIRST DEGREE RELATIVES OF THE MSELENI DWARFS

	MJD status of parents			
	Mother	Father	Siblings	Children
1	Unkown	Normal	No sibs	None
2	Affected	Normal	No sibs	One baby
3	Affected	Unknown	No sibs	None
4	Dwarfed	Unknown	Brother dwarfed	Three under 10 as yet normal
5	Affected	Normal	Brother dwarfed	Two under 5 years
6	Affected	Unknown	Dwarfed sister (18) Affected brother	All under 10 " as yet normal
7	Affected	Unknown	None	Three unaffected children
8	Unknown	Unknown	No sibs	None
9	Affected	Affected	Affected sister	Affected daughter
10	Affected	Unknown	An affected sister and 2 dwarfed brothers	None
11	Affected	Said to have been dwarfed	Dwarfed sister, affected brother	Both under 6 years
12	Affected	Unknown	Affected sister and brother	Four under 10 "
13	Affected	Unknown	A normal brother	None
14	Affected	Affected	Two dwarfed brothers, dwarfed sister, affected sister	None
15	Affected	Unknown	One affected sister	None
16	Affected	Unknown	One affected brother	Both under 6 years
17	Affected	Unknown	Affected brother	Two dwarfed children
18	Affected	Unknown	Sister of 6	Four under 8 years
19	Unsure	Unknown	None	None
20	Affected	Unknown	Affected sister	None
21	Affected	Unknown	Affected sister	Both under 8 years
22	Affected	Normal	Affected sister	None

TABLE (Continued)

	MJD status of parents			
	Mother	Father	Siblings	Children
23	Affected	Unknown	Affected sister	One baby
24	Affected	Said to have been dwarfed	Sister of 11	None
25	Unknown	Unknown	None	None
26	Affected	Affected	Affected sisters	Two under 6 years
27	Affected	Affected	Brother of 14	Four children, 10 years and under.

Family history: The first degree relatives of the 27 dwarfs are summarised in Table XXXVIII.Where the statement unknown is applied, the person was either dead, or an indefinite history was given by the respondent.

Three of the dwarfs are orphans, numbers 3, 8 and 25, and it is not known whether their parents were affected. They do not have siblings. Two are however first cousins to three and two other dwarfs respectively. The mother of dwarf 1 left home when he was a child. The father is unaffected. Dwarfs 11, 15, 24 and 27 appear in genealogy I; numbers 5, 10 and 21 are in genealogy 2; numbers 4, 14, 17 and 27 in genealogy 3; numbers 9 and 22 in genealogy 4; and numbers 13 and 16 in genealogy 5. Of those not mentioned this far, dwarfs 6 and 18 were sisters and first counsins of number 25. Their mother was affected by osteoarthrosis of a severe degree in multiple joints. Their father was dead but was said to have been affected.

The majority of these dwarfs have at least one parent who is affected by MJD. In 9 cases there is a dwarfed sibling.

Only 3 dwarfs had adult children. In one case both children were dwarfed, in one case a daughter had MJD. The 3 children of the third woman were said to be unaffected but they were not examined radiologically. In the case of the other dwarfs who had children, they were generally too young to state with certainty whether they were affected or not.

It is apparent therefore that the dwarfs are members of only six family groups within the Mseleni/Manaba population. There is thus a very strong familial element to the occurrence of dwarfism among this population.

General examination:

The dwarfs generally have the same symptoms as the undwarfed patient with MJD. They complain of pain and stiffness in the joints of the lower limbs, particularly the hips. They usually state that the pains began in early childhood. There is no specific appearance characteristic of the Mseleni dwarfs, as there is for certain other disorders such as achondroplasia, or mucopolysacchardosis IV.[129] However, affected individuals do have certain features in common.

Generally there is no abnormality of the facies and no characteristic body deformity. Hair, eyes, ears and nails are not abnormal. There is mild to moderate shortening of both trunk and extremities usually with a marked lumbar lordosis. Several have gross degrees of genu valgum (see Fig. 51) and a few have clubbed feet. Asymmetrical shortening of the legs was noted in a few individuals usually in association with subluxation of a deformed femoral head from a dysplastic acetabulum. (see Fig.52) Short thick digits were commonly associated with abnormal proportions of the finger lengths.

Physical development apart from height is generally good. The dwarfs are well muscled, sturdily built individuals and at least two of the men do heavy work in the road building crews.

There is nc indication of mental or sexual retardation and 20 of the 27 dwarfs are parents of at least one child. The others are not married. Clinically their appearance is not suggestive of any specific endocrine disorder such as hypothyroidism. While two had slight enlargement of

the thyroid, this was not palpable in the other dwarfs.

All systems were normal on examination with the exception of the skeletal system. Restricted range of movement at the hip joint was the most common orthopaedic finding while crepitus and restricted movement was also noted in the knees and ankles.

TABLE XXXIX : THE TYPES OF ABNORMALITY PRESENT IN VARIOUS JOINTS OF THE DWARFS ON RADIOLOGICAL EXAMINATION

Patient	Hip joint				Knee				Ankle			Spine						Elbow		Shoulder.	
	Dysplasia	Osteoarthrosis	Femoral head**	Acetabulum*	Dysplasia	Metaphyseal flaring	Abnormal fibula length	Osteoarthrosis	Dysplasia	Slant sign	Osteoarthrosis	Flattening	Irregularity	Notching	Humping	Wedging	Osteoarthrosis	Dysplasia	Osteoarthrosis	Dysplasia	Osteoarthrosis
1 MN	+	-	S	Sh	+	+	+	-	+	+	-	+	+	-	-	-	-	-	-	+	-
2 MM	+	-	M	I	+	+	-	-	+	-	-	-	+	-	-	-	-	0	0	0	0
3 DM	+	-	S	Sh	+	+	+	-	+	+	-	+	-	-	-	-	-	+	-	+	-
4 BM	+	-	M	Sh	+	+	-	-	+	+	-	+	-	-	-	-	-	+	-	+	-
5 NN	+	-	M	-	+	-	-	-	+	-	-	+	+	-	-	-	-	-	-	-	-
6 NM	+	-	M	I	+	-	-	+	+	-	-	+	-	+	+	-	-	0	0	0	0
7 MT	+	+	M	-	+	+	+	-	+	+	-	+	-	-	-	-	-	0	0	0	0
8 NK	+	-	S	Sh	+	-	-	-	+	+	-	+	+	-	-	-	-	-	-	-	-
9 SZ	+	+	S	Sh	+	-	-	-	+	-	+	-	+	-	-	-	-	+	-	+	-
10 NN	+	-	S	Sh	+	+	-	-	+	+	-	+	-	-	-	-	-	0	0	0	0
11 MM	+	+	S	Sh	+	+	-	-	+	+	-	+	-	-	+	-	-	+	-	+	-
12 GM	+	+	S	Sh	+	+	-	-	+	-	-	+	+	-	-	-	-	0	0	0	0
13 CN	+	-	M	Sh	+	+	-	-	+	+	-	+	-	-	-	-	-	+	-	+	-
14 GM	+	+	S	Sh	+	+	-	-	+	+	-	+	+	+	-	-	-	0	0	0	0

Key

+ = Abnormality present

- = Abnormality absent

0 = Not radiographed

Sh = Shallow

I = Irregular

D = Dysplastic

M = Microepiphyseal**

S = Squared or hatchet shaped.**

TABLE XXXIX (Continued)

Patient		Hip joint				Knee				Ankle			Spine						Elbow		Shoulders	
		Dysplasia	Osteoarthrosis	Femoral head**	Acetabulum*	Dysplasia	Metaphyseal flaring	Abnormal fibula length	Osteoarthrosis	Dysplasia	Slant sign	Osteoarthrosis	Flattening	Irregularity	Notching	Humping	Wedging	Osteoarthrosis	Dysplasia	Osteoarthrosis	Dysplasia	Osteoarthrosis
15	VM	+	-	D	-	+	-	-	-	+	-	-	-	-	-	+	-	-	+	-	+	-
16	NS	+	-	M	Sh	+	+	+	-	+	+	-	+	+	-	-	-	-	0	0	0	0
17	GM	+	+	S	Sh	+	-	-	+	+	-	+	+	-	+	-	-	-	-	+	-	+
18	FM	+	+	S	I	+	+	-	-	+	-	-	-	-	-	-	-	-	0	0	0	0
19	NM	+	-	M	Sh	+	+	+	-	+	-	-	+	+	-	-	-	-	0	0	0	0
20	SG	+	+	S	Sh	+	-	+	-	+	-	-	+	+	+	-	-	-	0	0	0	0
21	NS	+	+	S	-	+	-	-	-	+	-	-	+	-	-	+	-	-	0	0	0	0
22	PS	+	-	D	-	+	-	-	-	+	-	-	+	+	-	-	-	-	0	0	0	0
23	LS	+	-	D	-	+	-	-	-	+	-	-	-	+	+	-	-	-	0	0	0	0
24	MM	+	+	M	Sh	+	-	-	-	+	-	-	+	+	-	-	-	-	0	0	0	0
25	MM	+	+	S	-	+	+	-	-	+	+	-	+	+	-	+	-	-	0	0	0	0
26	NM	+	-	S	Sh	+	-	-	-	+	-	-	+	+	-	-	-	-	0	0	0	0
27	MM	+	-	S	Sh	+	+	+	-	+	+	-	+	-	-	-	-	-	0	0	0	0

Key

+ = Abnormality present

- = Abnormality absent

0 = Not radiographed

Sh = Shallow *

I = Irregular *

D = Dysplastic*

M = Microepiphyseal**

S = Squared or hatchet shaped. **

TABLE XXXX : ABNORMALITIES PRESENT IN HAND RADIOGRAPHS OF THE DWARFS

Person	Short metacarpals										Bone deformities						
	Left hand					Right hand					Carpals		Radius		Ulna		Phalanges
	1	2	3	4	5	1	2	3	4	5	Left	Right	L	R	L	R	
1 MN	++	+	++	++	-	++	+	++	++	-	++	++	++	++	++	++	-
2 MM	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	Generalised abnormality
3 DM	++	++	++	++	++	++	++	++	++	++	++	++	+	+	++	++	-
4 BM	++	+	++	++	++	++	+	+	++	++	++	++	++	++	++	++	-
5 NN	-	-	+	-	-	-	+	+	-	-	-	-	++	++	+	-	Generalised abnormality
6 NM	++	-	+	+	+	++	-	++	++	++	++	++	++	+	+	+	-
7 MT	++	-	+	+	-	++	-	+	+	-	++	++	+	+	+	-	I.P. dysplasia
8 NK	+	-	++	++	-	+	-	++	++	-	++	++	++	++	++	++	-
9 SZ	-	-	-	-	-	-	-	-	-	-	++	++	-	-	+	+	-
10 NN	++	-	-	+	-	++	-	++	+	-	++	++	++	++	++	++	-
11 MM	++	+	++	++	-	++	+	++	++	++	++	++	++	++	++	++	-
12 GM	++	-	-	-	-	+	-	-	-	-	++	++	++	++	++	++	-
13 CN	++	+	-	-	+	++	-	++	-	++	+	+	++	+	+	+	-
14 GM	++	-	++	++	-	++	*	++	++	-	+	+	+	+	+	+	-
15 VM	++	++	++	-	+	++	-	++	++	++	++	++	+	+	++	+	-
16 NS	++	-	-	-	-	-	-	-	-	-	++	++	+	+	+	+	-
17 GM	-	-	-	-	-	-	-	-	-	-	++	++	++	++	++	++	-
18 FM	++	+	+	++	-	+	-	+	-	-	++	++	-	-	-	-	-
19 NM	++	+	+	+	+	+	+	+	+	+	++	++	+	+	+	+	-
20 SG	-	-	-	-	-	-	-	-	-	-	-	-	+	+	+	+	-
21 NS	+	-	-	-	-	+	-	-	-	-	++	++	+	+	++	+	-
22 PS	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
23 LG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24 MM	+	-	-	-	+	++	-	-	-	-	-	-	-	-	-	-	-
25 MM	++	-	-	-	-	++	-	-	-	-	++	++	++	++	++	++	Generalised abnormality
26 NM	++	-	-	-	-	++	-	+	-	-	++	++	+	+	+	+	-
27 MM	++	+	++	++	++	++	-	++	++	++	++	++	++	++	++	++	-

TABLE XXXXI : ABNORMALITIES PRESENT IN THE FEET RADIOGRAPHS OF THE DWARFS

Person		Short metatarsals										Bone deformities				
		Left foot					Right foot					Tarsals		Metatarsal dysplasia.	Phalanges	Other
		1	2	3	4	5	1	2	3	4	5	L	R			
1	MN	++	++	++	++	++	++	++	++	++	++	++	++	++	-	-
2	MM	++	++	++	++	++	++	++	++	++	++	+	+	++	+	-
3	DM	++	++	++	++	++	++	++	++	++	++	+	+	++	-	-
4	BM	++	+	+	+	+	++	+	+	+	+	+	+	+	-	*2
5	NN	-	-	-	-	-	-	-	-	-	-	-	-	+	-	*2
6	NM	+	-	+	-	+	++	++	+	++	+	++	++	++	+	
7	MT	++	+	+	+	+	++	+	+	+	+	++	++	++	+	
8	NK	-	-	-	-	-	-	-	-	-	-	+	+	+	-	-
9	SZ	+	-	-	-	-	+	-	-	-	-	+	+	+	+	*2
10	NN	-	-	-	++	-	-	-	+	+	+	++	++	++	-	
11	MM	++	++	++	++	++	++	++	++	++	++	-	-	++	-	-
12	GM															
13	CN	++	++	++	++	-	++	++	++	++	++	+	+	++	-	-
14	GM	++	++	++	++	++	++	++	++	++	++	+	+	++	-	*1*2
15	VM	+	++	++	++	+	+	++	++	++	+	++	++	+	-	
16	NS	++	++	++	++	-	++	-	++	++	-	-	+	+	-	-
17	GM	+	-	-	-	-	+	-	-	-	-	+	+	-	-	
18	FM	+	-	-	-	-	+	-	+	-	-	+	-	++	-	
19	NM	++	+	+	+	+	+	+	+	+	+	+	+	++	+	*2
20	SG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
21	NS	+	-	-	-	-	-	-	-	-	-	-	-	++	-	-
22	PS	++	-	-	-	-	+	-	-	-	-	+	+	++	-	-
23	LS	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-
24	MM	++	-	-	-	-	+	-	-	-	-	-	-	+	-	-
25	MN	++	-	+	+	+	++	-	+	+	+	+	+	++	-	-
26	NM	+	-	-	-	-	+	-	-	-	-	+	+	+	-	-
27	MM	++	++	++	++	+	++	++	++	++	++	++	++	++	-	-

- Normal length + shortened ++ Very short - Normal + Abnormal
++ Grossly abnormal

*1 Cuboids fused into single block
*2 Digits overlapping

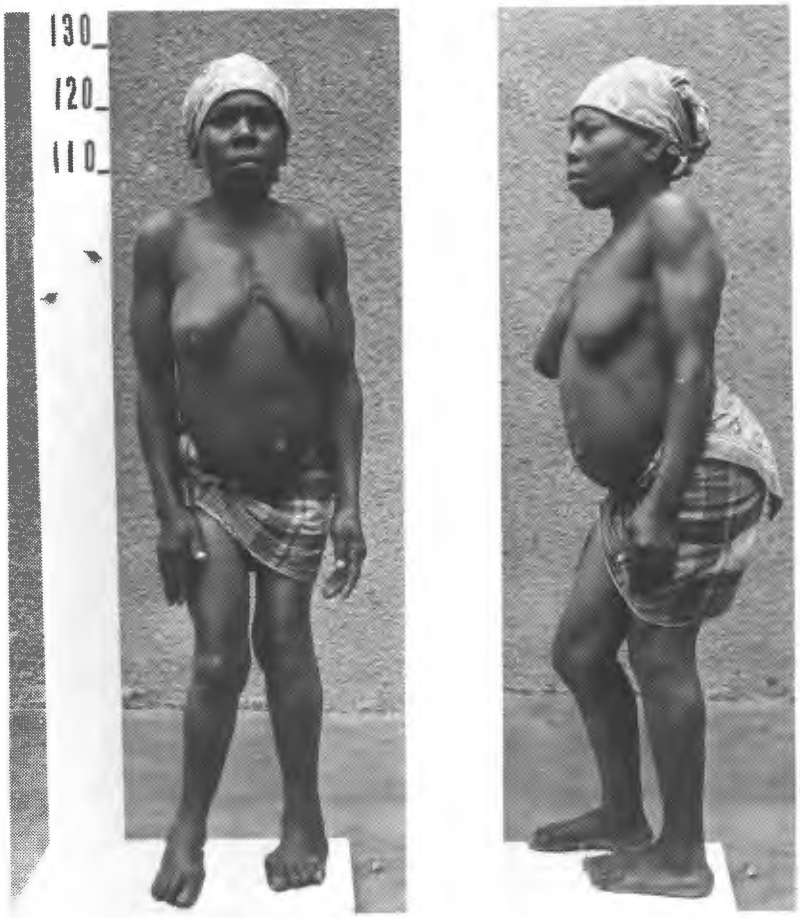
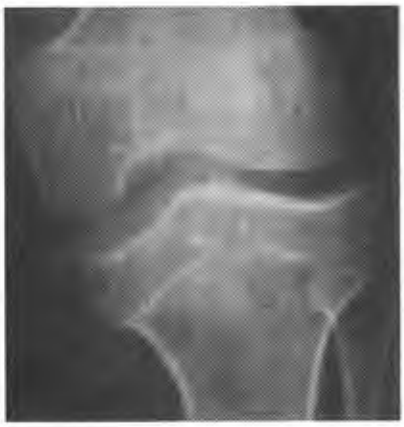


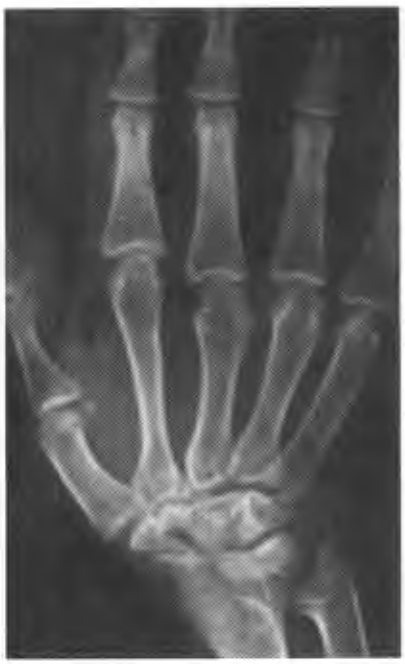
Fig. 54: Dwarf N.N. No. 5. Subject IV 33 from Genealogy II.

A. her spine
B her knee
C her hand
D her ankle
E her foot

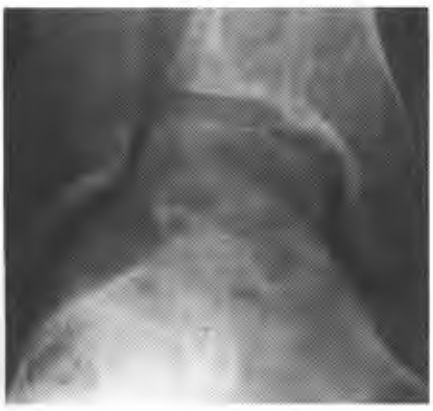
A



B



C



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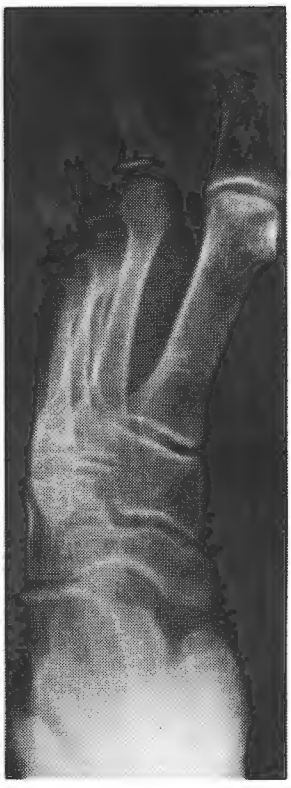

E

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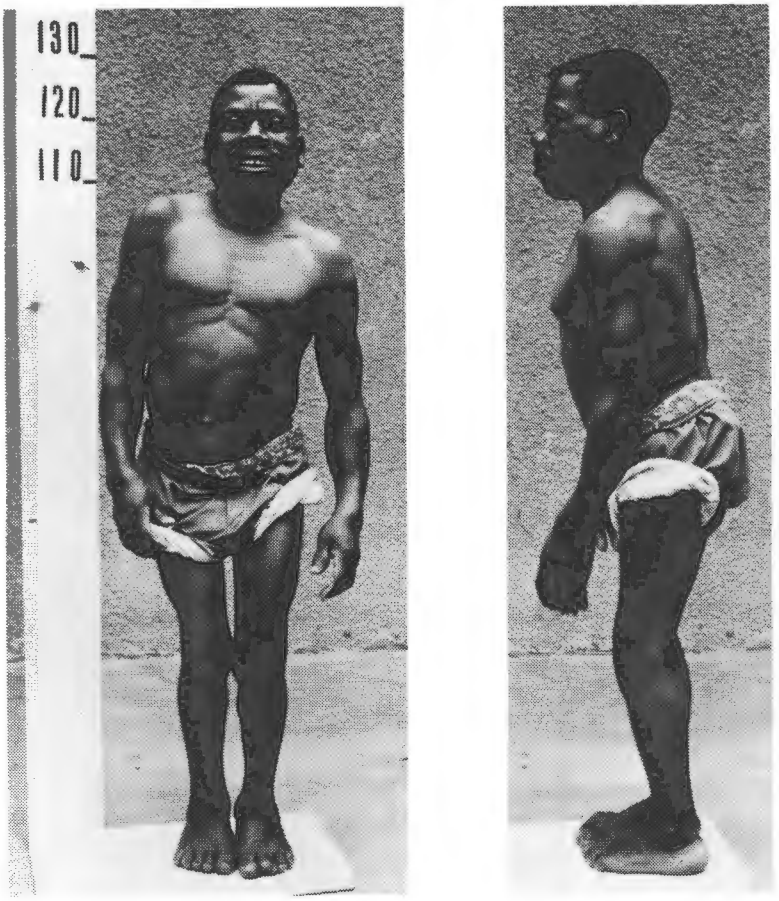
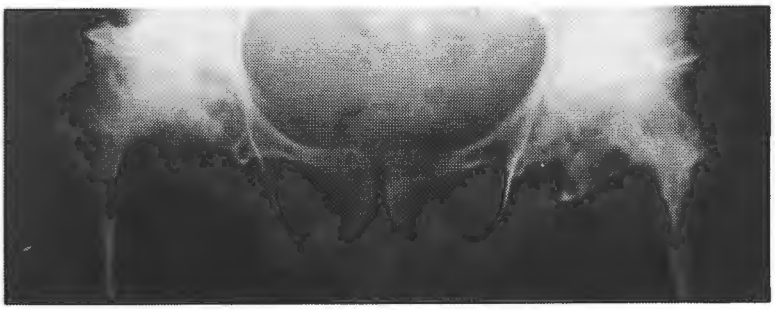
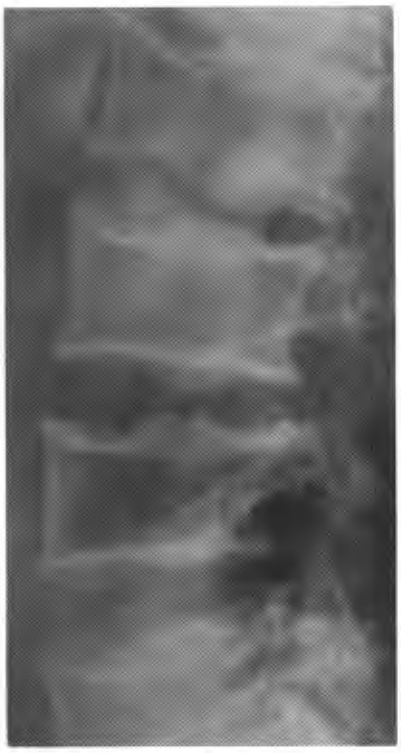


Fig. 55: Dwarf M.M. No. 11. Subject III 53 in Genealogy I

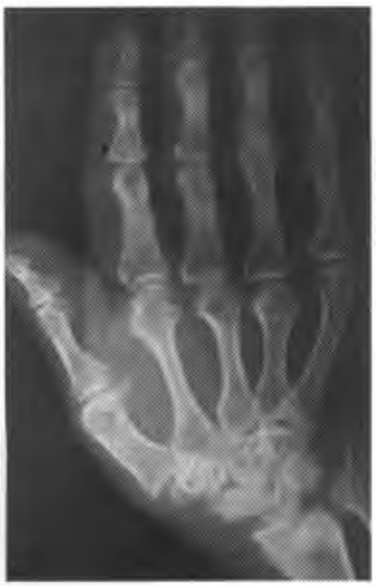
A his spine
B his hips
C his hand
D his ankle
E his knee



B

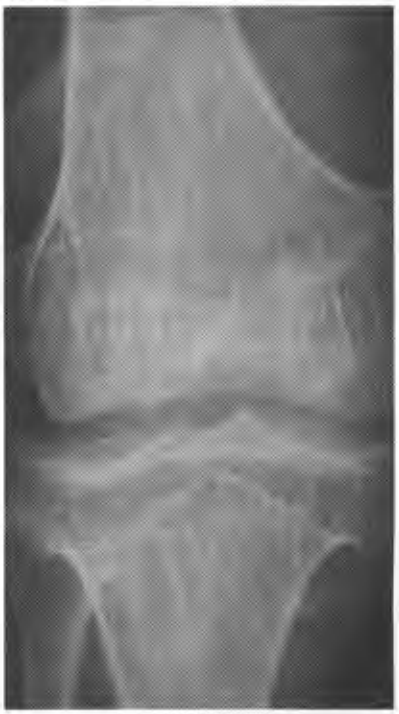


A



C

D



E

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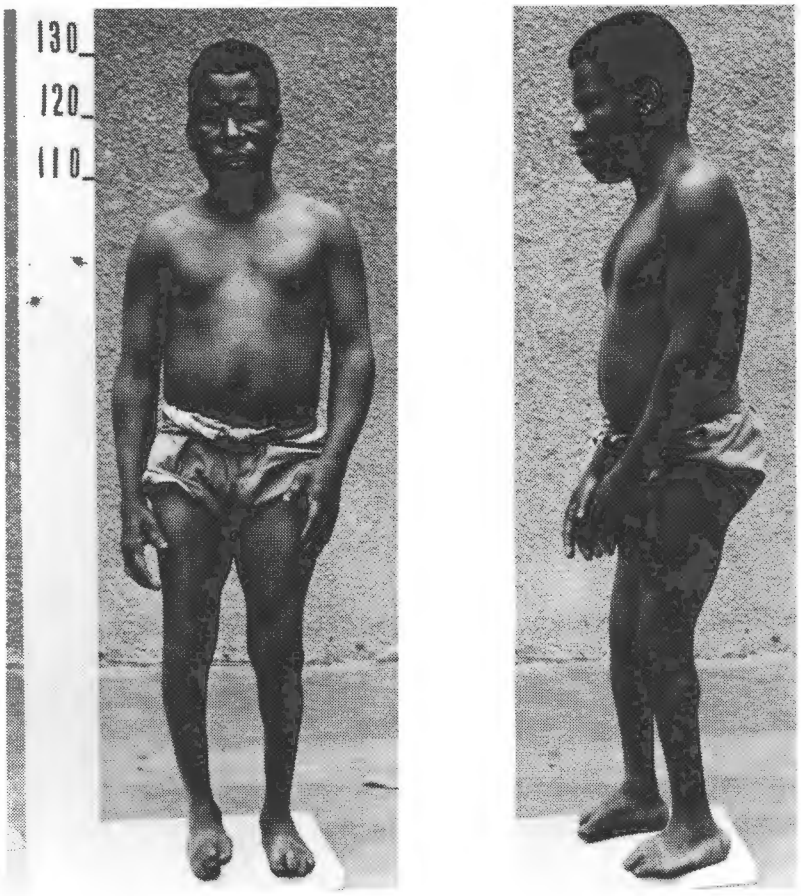
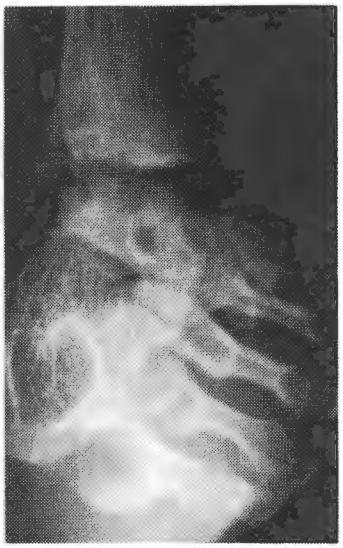
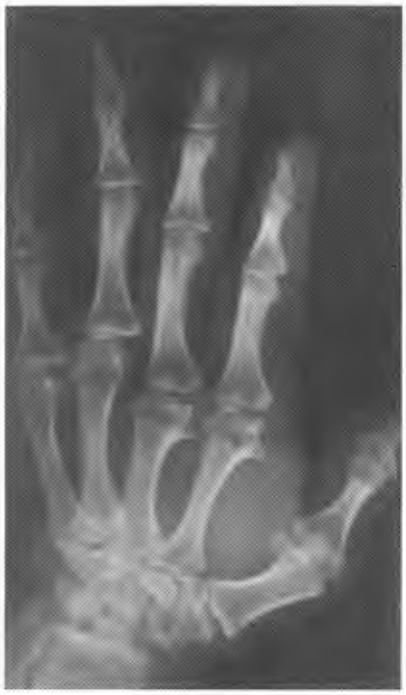


Fig. 56: Dwarf V.M. No. 15. Subject III 36 in Genealogy I.

A his ankle
B his hand
C his foot
D his spine
E his hips



A



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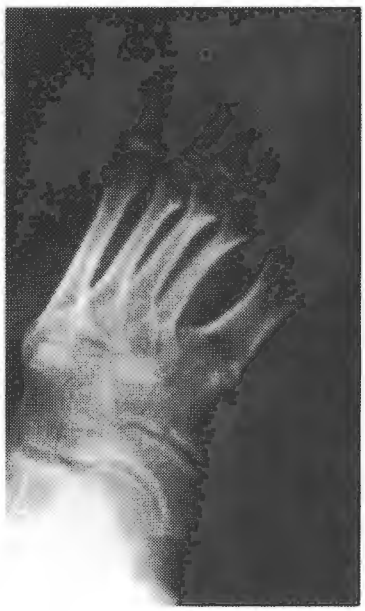

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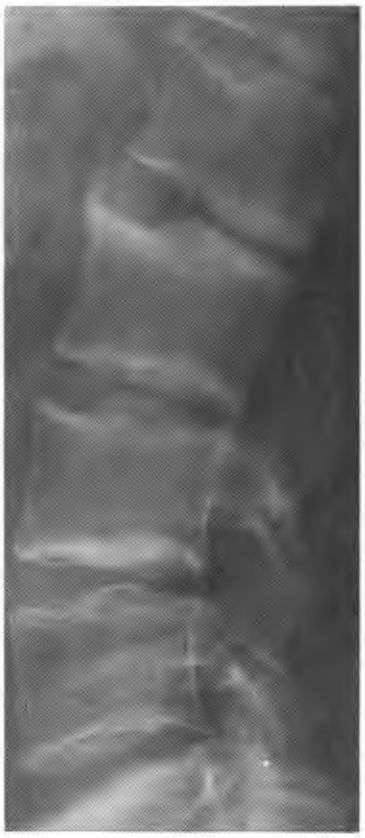

D

E

-GAcsir 01HL2172*174

THE RADIOLOGICAL APPEARANCE OF THE JOINTS IN THE MSELENI DWARF

The joints of the dwarf with Mseleni Joint Disease show the same type of abnormality as seen in the child, namely, epiphyseal dysplasia, but the abnormality is far more severe, metaphyseal involvement is usually present and deformities are amplified. The findings in each joint for the dwarfs examined are seen in Tables XXXIX, XXXX and XXXXI.

The typical abnormalities are illustrated for three of the dwarfs. Dwarf No. 5, a mother of 2, is seen in Fig. 54 ; and Figs 54A, B, C, D and E show her spine, knee, hand, foot and ankle, respectively. Dwarf No. 11 is shown in Fig. 55, and Figs, 55A, B, C, D and E shows his spine, hip joints, hand, ankle and knee, respectively. Dwarf No. 15 is seen in Fig. 56 while Figs. 56 A. B. C, D and E show his hand, ankle, foot, hips and spine, respectively.

THE JOINT ABNORMALITIES

The hip joint typically shows a mushroomed micro-epiphyseal femoral head often associated with a shallow dysplastic acetabulum. The iliac crest has no consistently abnormal form. The sacro-iliac notch is not narrowed. The pubic synchondrosis is often grossly irregular. Fairly advanced osteoarthritic changes were seen in the hips of 9 of the dwarfs.

The knee joint shows a marked irregularity of the articular surface with flaring or trumpeting of the metaphysis present in about half the cases. This metaphyseal flare was not seen in any MJD cases of normal stature.

The ankles may simply show articular irregularity, or may have the oblique talus and tibia (or tibial slant sign) originally said to be typical of multiple epiphyseal dysplasia.[55] This slant sign was present in just less than half the dwarfs, and was not seen to such a marked degree in any adults of normal stature.

Marked osteoarthrosis had supervened in only 2 cases.

ELBOW

The elbow was abnormal in 7 of the 10 dwarfs in whom it was examined. Six showed epiphyseal dysplasia and one osteoarthrosis.

SHOULDERS

These were abnormal in eight of the ten dwarfs in which the shoulders were examined.

HANDS

The carpal bones were very deformed in 20 cases and moderately abnormal in two. In five dwarfs they were normal.

The distal ends of radius and ulna were normal in only 4 subjects, while one dwarf had abnormal ulnae with normal radius.

Very stunted thick metacarpals were a prominent feature. Normal metacarpals were seen in only five dwarfs.

Three dwarfs showed a generalised abnormality of the phalanges which had very squared and flattened heads, one had multiple irregularity

of phalangeal heads and in the remaining 24, the phalanges were normal.

FEET

Radiographs were available for 26 of the dwarfs. In none were the feet completely normal. Short metatarsals were seen in all but four. Tarsal deformities were present in 19, metatarsal dysplasia was present in 24 and phalangeal abnormalities in 5. In five cases there was marked metatarsal abduction with overlapping of bones, while in one case the cuboids were fused into a single block of bone.

SPINE

The radiograph of the thoracic-lumbar spine revealed abnormalities varying from platyspondyly to posterior humping of the vertebral body, often associated with irregularity of the superior and inferior borders of the vertebral body.

Posterior humping of the vertebral body resembling that described for X-linked spondylo-epiphyseal tarda[101] was seen in 4 dwarfs, 2 of whom were females. Generalised platyspondyly was seen in all but 5. These 5 showed marked end plate irregularity and notching.

No abnormality has been noted on skull radiographs in the 5 dwarfs where the skull was examined.

TABLE XXXXII : THE IMPORTANT BIOCHEMICAL PARAMETERS MEASURED ON THE DWARFS[29a]

PERSON	(mU/ml) Alk. phospha-tase.	(mU/ml and phospha-tase.	Fe (ppm)	Cu (ppm)	Zn (ppm)	(mg/100 ml) Mg	(mg/100 ml) Trans-ferrin	(mg/100 ml) Caerulo-plasmin	Ca mg(100 ml)	Inorganic phosphate mg/100 ml
NORMAL VALUES:	38-138	0-11	0,7-1,3	1,1-2,0	0,8-1,4	1,0-3,0	200-400	20-40	9 - 11	2,5-4,8
2 MM	40,0	10,2	0,96	1,48	0,90	1,36	213,0	40,54	9,14	3,18
3 DM	45,3	11,72	1,04	1,56	0,64	1,66	266,5	36,20	9,52	3,85
5 NN	46,8	11,31	1,48	1,62	0,66	1,40	205,0	36,58	9,08	4,00
7 MT	42,2	9,44	1,54	2,16	0,92	1,95	222,5	49,60	8,80	4,06
9 SZ	52,5	9,39	0,84	2,20	0,98	0,90	286,0	58,36	9,84	4,90
10 NN	43,6		1,24	1,68	0,86	1,15	267,5	44,50	8,74	3,91
11 MM	40,6	7,47	0,88	1,66	0,74	1,50	295,0	40,50	8,64	4,10
12 GM	43,0	9,29	1,02	1,64	0,82	2,50	195,5	40,0	9,50	3,96
14 GM	35,3	9,10	1,26	1,92	0,76	1,50	267,5	41,90	8,34	3,08
15 VM	46,3		0,96	1,48	0,90	1,13	282,5	35,30	9,02	3,89
16 NS			1,84	1,52	0,78	1,47	325,0	36,58	8,80	4,42
21 NS	72,3	17,2	0,84	2,16	0,76	1,80	336,0	52,06	9,84	4,70
24 MM	40,4		1,36	1,38	0,78	1,10	275,5	43,28	8,94	3,05

SPECIAL INVESTIGATIONS

Investigations were carried out on a number of the dwarfs but for logistic reasons not all studies could be performed on all the individuals and several necessary investigations have not as yet been carried out.

Routine parameters investigated include haematocrit, E.S.R., differential white cell count, red cell and platelet morphology, total and individual serum proteins, magnesium, sodium, chloride, and bicarbonate values.

Other investigations included parameters referable to bone metabolism, i.e. calcium, inorganic phosphate, acid and alkaline phosphatases, as well as certain trace elements. Iron, copper, zinc and magnesium and the carrier proteins, transferrin and caeruloplasmin were measured on 13 of the dwarfs. The results are shown in Table XXXXII. No significant abnormalities were present. Specifically the serum calcium, phosphate and alkaline phosphatase were within normal limits.

Screening tests for inborn errors of metabolism were carried out on urine from 12 of the dwarfs. The tests were negative for a range of substances including homogentisic acid and mucopolysaccharides, reducing substances, ferric chloride, ketones, sulfur containing amino acids, tyrosin metabolites, proline and copper[29a].

Further tests for urinary mucopolysaccharides were carried out on dwarfs. No abnormal mucopolysaccharides were found with any of the 6 different tests used[15].

Chromosome studies carried out on 8 dwarfs revealed normal karyotypes.

SUMMARY OF RESULTS

There is no specific appearance characteristic of the Mseleni dwarfs. Facies, skull, eyes, ears, hair and nails are not abnormal.

There is a range of heights from slightly stunted growth, 151 cms to very severe dwarfism, 117 cms (adult height). In general all have some degree of trunk and limb shortening, a lumbar lordosis, and varying degrees of genu valgum or misshapen hands and feet.

The only abnormalities are those referable to the skeletal system and specifically to the joints. The radiological appearance of the joints was that of a very severe degree of epiphyseal or epiphyseal-metaphyseal dysplasia, similar to but of greater severity than that in a non-dwarfed person with MJD.

No chromosomal or biochemical abnormality has been found.

DISCUSSION OF THE DWARF STUDIES

The problem of dwarfism among the Mseleni population will be discussed in detail, as the author believes the dwarfs to be of great significance to the Mseleni problem.

Dwarfism may be defined as a condition in which the height of an individual is less than that which is 3 standard deviations below the mean height for age[172].

Bailey[7] considers absolute shortness of stature to be 152 cms (5') or less for males and 147 cms (4' 10") for females. Silverman[162] included as "little people" all adults with a mature height of 152,4 cms or less and defined a dwarf as an individual whose mature height is less than 132 cms (4' 6"). These criteria, however, relate to American standards.

With reference to the Mseleni population, the average height among 64 unaffected adult males was found to be 165 cms (5' 6") while the height of 7 affected males was little different. (Section III.2.2).

A standard of 152 cms for absolute shortness in males would seem appropriate as a criterion for Mseleni. This is a difference of 13 cms between that and the average height of Mseleni males.

Among the population of the affected area who were personally seen by the author, 6 men could be classified into this group.

The average height among 56 normal adult women in the Mseleni population was however 155 cms, and that of 31 affected women, significantly

lower, 150 cms. Bailey's standard of 147 cms as absolute short stature is perhaps slightly high with reference to the Mseleni population and I have chosen to use a level of 142 cms in women as a criterion for absolute shortness of stature. This again provides a difference of 13 cms between that criterion and the average height of normal woman. Comparisons can therefore readily be made between the number of male and female "little people".

Altogether 12 male dwarfs and 28 female dwarfs were identified. Because the method of ascertainment this probably represents all the adult dwarfs in the area, although one or two who have left the area to work may have been overlooked. It was considered too difficult to detect dwarfism among the younger children as this would have involved a subjective judgement on the part of the field-workers which was unlikely to have been accurate for moderate degrees of stunting. One obviously dwarfed 15 year old was observed by the author and has been included in this series.

The causes of short stature

Short stature may be physiological or pathological. An example of physiological dwarfism is that of the dwarfed race of Pygmies who are genetically small in stature[173].

Pathological short stature may be due to one of three causes. An environmental factor acting on a genetically sound constitution, a genetically determined abnormality of one or more body systems, or a combination of genetic disorder and environmental effects.

Each of these causes may produce dwarfism which may be of intra-uterine onset, therefore congenital and obvious at birth, or which may only become apparent at a later date. Of importance here are those factors producing dwarfism of postnatal onset. A brief classification of such factors is listed below:

Factors producing short stature of post natal onset[173].

1. Germ cell anomalies:
   (a) genetic disorders
   (b) chromosomal anomalies

2. Environmental factors:
   (a) Malnutrition;
   (b) chronic infections;
   (c) trace element deficiencies;
   (d) drugs and toxins.

3. Multifactorial: Cardiac, pulmonary, venal, hepatic, endocrine or metabolic disorders of varying causes.

In the differential diagnosis of the aetiology of the Mseleni dwarfism the group of chronic, cardiac, pulmonary, renal, hepatic and metabolic diseases can be excluded as no evidence of such disorders has been found in the Mseleni dwarfs. There is also no indication that any overt endocrine disorder, such as hypothyroidism is prevalent in this area.

Although the Mseleni population are malnourished by western standards they are generally not more so than the surrounding populace. Rickets

is seldom seen.

Schistosomiasis and malaria are endemic in the area but are equally so in the surrounding areas. Tuberculosis is also common among the Mseleni population and in the surrounding areas. Chronic infection, while producing stunting of growth would not produce the extreme disproportional dwarfism seen in several of the Mseleni dwarfs.

Trace element deficiencies, particularly zinc, are known to produce dwarfism[173]. No indication of trace element deficiency was detected at the present time in the dwarfs or the children tested. Specifically, both zinc and magnesium were found to be normal. No toxins have as yet been identified as part of the Mseleni diet, but this aspect has still to be fully investigated and will not be discussed here.

At the present time, therefore, the emphasis is on those germ cell anomalies, genetic or chromosomal, which produce dwarfism of post-natal onset with skeletal abnormalities in the absence of abnormalities of other systems such as cardiovascular or pulmonary. These are the conditions which may be grouped together under the heading of skeletal or osteochondro-dysplasias.

Short stature disorders considered in the Mseleni context

The Mseleni dwarfism may be classified with the conditions of disproportional short stature. It is probably of late onset but as the dwarfs observed were adults, it is not known if they were normal at birth. Abnormal findings are restricted to the skeletal system.

There are a number of conditions causing disproportionate short stature which were considered in the differential diagnosis of the Mseleni dwarfism. These will be briefly discussed.

Achondroplasia[102] is the most common type of short limb dwarfism, recognisable at birth and easily differentiated in the adult from the other forms of dwarfism[161]. It is characterised by marked short limbed dwarfism, a large head with low nasal bridge and prominent forehead, short trident hands and lumbar lordosis. In a survey of 101 individuals with achondroplasia, Langer[102] stated that about 5% did not show absolutely classic clinical features although all showed signs strongly suggestive of the disease. However, all showed the roentgenographic features which he designated as typical, which included a progressive caudate narrowing of the interpedicular distance in the lumbar spine, small iliac wings with a narrow greater sciatic notch, shortened tubular bones with metaphyseal flare and ball and socket appearance of epiphysis and metaphysis. The inheritance is autosomal dominant but about 90% of cases represent a new mutation[164].

On a basis of the clinical and radiological features, it is evident that the Mseleni dwarfs do not belong to the achondroplasia group.

Hypochondroplasia[171] is an autosomal dominant inherited disorder characterised by mild short limbed dwarfism not obviously apparent at birth. The skull is normal and the hands and feet are short but relatively normal in appearance. A lesser degree of caudate spinal narrowing is seen than in achondroplasia.

The multiple dysplastic involvement of epiphyses in the Mseleni patients differentiate them from this condition.

Diastrophic dwarfism is the term suggested by Lamy and Maroteaux [100] (1960), to designate a form of dwarfism characterised by twisted lower extremities and varying degrees of scoliosis. The condition may be suspected at birth by the presence of multiple skeletal anomalies such as clubbed feet, dislocated hips and knees, crooked fingers, scoliosis and/or kyphosis and low-set ears with soft cystic masses in the auricles.

It is an autosomal recessive condition. Although a few of the Mseleni dwarfs have a mild scoliosis and two have clubbed feet, the Mseleni dwarfs clearly do not have this disorder.

The term Metatrophic dwarfism was suggested by Maroteaux et al.[119], (1966), to describe a severe form of dwarfism characterised by a marked change in relative body proportions from birth to adult life. The neonate with short limbs and a relatively long trunk resembling an achondroplastic dwarf, develops into an adult with normal head, very short trunk with deformed kyphoscoliotic spine, protruding sternum and relatively long limbs.

Inheritance is believed to be autosomal recessive. The Mseleni dwarfs do not have the stigmata of metatrophic dwarfism.

Metaphyseal dysostoses or metaphyseal chondrodysplasia are a group of conditions characterised by short limbed dwarfism with clinically normal appearing head, hand, face and bow legs[161].

On X-ray, irregularity, sclerosis and areas of rarifaction or radiolucent defects are seen in the metaphysis of the long tubular bones and some flaring of metaphyseal margins may be seen. There are at least four subtypes of conditions included in this group. The majority of Mseleni dwarfs have some degree of metaphyseal involvement but the predominantly epiphyseal lesions again differentiate these dwarfs from those with the metaphyseal chondrodysplasias.

Dyschondrosteosis[173] is characterised by mild to moderate short stature, and foreshortened extremities with bilateral Madelung deformity. Dislocation of the distal radio-ulnar joint causes limitations of movement of the wrist. The mode of inheritance is autosomal dominant but the literature records an unexplained excess of affected females.

In dyschondrosteosis, epiphyses of the major joints other than those of the radius and ulna are usually normal. This is unlike Mseleni dwarfism. The abnormalities of the radius and ulna in the Mseleni dwarfs, though resembling a Madelung deformity in several instances, do not conform to the criteria of a true Madelung deformity, neither is an abnormal radius and ulna seen in all of the Mseleni dwarfs. The diagnosis of dyschondrosteosis may therefore be excluded from further consideration.

The multiple epiphyseal dysplasias (MED) and spondylo-epiphyseal dysplasia (SED) are a group of conditions characterised by abnormalities of bone growth affecting multiple epiphyses of the long bones, as well as the short tubular and round bones, with varying spinal involvement[7,115]. These disorders have been grouped into "congenita" forms which are recognisable at birth and "tarda" forms in which the characteristic manifesta-

tions, appear later.

These are a heterogeneous group of conditions characterised by irregularity of density and form of multiple epiphyses resulting in adults of either normal or dwarfed stature. In the MED group spinal involvement is variable and platyspondyly is not a feature.

The SED group are also characterised by multiple epiphyseal abnormalities but in these conditions spinal abnormalities are marked and platyspondyly is a prominant factor.

All but one of the Mseleni dwarfs have some degree of spinal involvement. In just over half a pronounced platyspondyly, as seen in the SED group of conditions, is present while the remainder manifested the vertebral irregularity and notching with minimal height reduction seen in the MED group. Furthermore, metaphyseal involvement occurs in over half the cases.

While persons with epiphyseal dysplasia may be placed into either the MED or SED group on the basis of the degree of spinal involvement, it is apparent that within these two categories there is much overlap. Families have been reported in which certain members would be classified as affected by MED and yet other members are typical of the SED group[173]. In the Mseleni situation there are patients with the stigmata of MED, and others who clearly have SED.

It is apparent that on the basis of the radiological findings in

this group of dwarfs, the Mseleni dwarfs would be classified into the MED and SED group of conditions, but attempts to further categorise their disorder would fulfil no useful purpose at this stage.

THE RELATIONSHIP OF THE DWARFISM TO MSELENI JOINT DISEASE

The symptoms described by the dwarfs were like those of the MJD cases with normal stature with the exception that most of the dwarfs stated that the pain and stiffness had begun in early childhood.

Most of the dwarfs had first degree relatives who were not dwarfed but had MJD.

The radiological findings in the dwarfs were a more pronounced form of the abnormalities seen in the non dwarfed cases. It, therefore, appears that the dwarfs represent the more severely affected cases in which the disease manifests early and produces more severe stunting of bone growth. This could be due to a greater and earlier exposure to an environmental factor or if MJD is of genetic aetiology, to a homozygous state for the abnormal gene or a greater degree of expressivity.

HOMOZYGOSITY FOR MJD

If we consider the dwarfs to represent the homozygous form of a dominant inherited disease, the implications will vary according to whether the inheritance is autosomal or X-linked. (See Table XXXXIII)

Autosomal dominant

A dwarf will then have the genotype MM and depending on the genotype of the mate, all the offspring will be either dwarfed or affected, and no sex difference should be apparent.

TABLE XXXXIII : DISEASE STATUS OF THE OFFSPRING OF A DWARF WHERE THE DWARF REPRESENTS THE HOMOZYGOUS STATE OF A DOMINANTLY INHERITED DISORDER

Inheritance	Geno-type	Sex of dwarf	Disease status of mate	Daughters	Sons
Autosomal sominant	MM	Male or female	1. Normal 2. Affected 3. Dwarf	All affected Half affected, half dwarfed All dwarfed	All dwarfed Half affected, half dwarfed All dwarfed
X-linked dominant	X^mY	Male	1. Normal 2. Affected 3. Dwarfed	All affected Half affected, half dwarfed All dwarfed	All normal Half normal, half dwarfed All dwarfed
X-linked dominant	X^mX^m	Female	1. Normal 2. Dwarfed	All affected All dwarfed	All dwarfed All dwarfed

A dwarf of either sex would have to be descended from two affected parents. In addition, at least one quarter of the offspring of a mating between two affected people should be dwarfed.

X-Linked dominant

Here the male will show the trait in the hemizygous form and, therefore, all males with the gene should be dwarfed. The female dwarf may be heterozygous for the gene. A sex difference among the offspring in respect of disease status should be observed. There will, of course, be no normal daughters of either the male or female dwarf. However, should a dwarfed male marry a normal woman, all their sons would be normal. If, however, the dwarfs represent simply a manifestation of greater expressivity, a dwarf would simply be considered as an affected person, whether homozygous or heterozygous, and the offspring frequencies tabulated in Tables XXXII and XXXIII would apply.

It is obvious that simple X-linked dominance can be excluded as the majority of the affected men are not dwarfed.

First degree relatives of the dwarf

In only one instance was a reportedly normal parent of a dwarf examined radiologically. He was found to be normal.

Only two dwarfs had adult offspring who were examined radiologically. Of these three adult offspring, one was a dwarfed female, one an affected female, and the third a fifteen year old normal boy.

Therefore it is probable that the dwarfs do not represent a homozygous form of MJD.

C O N C L U S I O N

The dwarfs are affected by a disorder which would be classified on radiological grounds into the MED/SED group of conditions. It is probable that the dwarfs do not represent a homozygous form of MJD but they may represent a greater degree of expressivity of an abnormal gene or alternatively the product of an earlier, prolonged and more intensive exposure to an abnormal environmental agent.

III.2.6 A STUDY OF AFFECTED PEOPLE LIVING OUTSIDE THE HIGH PREVALENCE AREA

III.2.6 A STUDY OF AFFECTED PEOPLE LIVING OUTSIDE THE HIGH PREVALENCE AREA.

During the course of the original epidemiological survey, possible cases of joint disease were discovered as far away as Maputa, and in Lake Sibaya around the north eastern corner of the lake. These people usually complained of joint pains and stiffness. It was thought that any possible connections with the high prevalence area should be investigated as this would add to the evidence for an hereditary or environmental basis for MJD.

M E T H O D S

For reasons of logistics a single area was selected which was within a few hours driving time from the Mission Hospital and yet which was thought to have a low prevalence rate for MJD. The area selected was sections 7 and 8 of the Lake Sibaya region (See Fig. 3).

DETERMINATION OF THE PREVALENCE RATE

A complete kraal by kraal enumeration of Sibaya sections 7 and 8 was carried out by one of the State Health Inspectors (as described in section II. 4.3). For each person listed, a family history form was completed and radiographs of the hips, hands and knees were taken. The author than examined each of these "affected" people. On the basis of the clinical and radiological examination, each person was assessed as affected or unaffected by MJD. The percentage of positive cases in the two sections was then calculated.

TABLE XXXXIV : SUBJECTS FROM SIBAYA SECTION 7 ENUMERATED AS HAVING MSELENI JOINT DISEASE (MJD)

Person		Sex	Age	History.	Radiograph of hips.	Radiograph of knees	Radiograph of hand.	Comment
1	MM	F	45	Pain in hips for about a year. Walks normally	Minimal protrusio acetabulae	Normal	Normal	Doubtful
2	MM	F	52	Pain in hips, knees, ankles for years. Typical MJD gait	Bilateral severe OA	Bilateral severe OA	Deformity. OA	MJD +
3	KM	F	26	Pain in hips, knees ankles since childhood.	Epiphyseal dysplasia - gross degree.	Epiphysiometaphyseal dysplasia.	Deformity	MJD +
4	NM	F	59	Pain in hips, knees, ankles since fourth child was born	Bilateral gross osteoarthritis	Bilateral OA	Mc, Mc/P IP and carpal OA	MJD +
5	NG	F	62	Pain in hips and knees for years.	Gross OA with very marked protrusio.	Normal	Normal	MJD +
6	SN	F	48	Pain in right hip only. Son and husband had TB.	Gross destruction of right hip. Left normal.	Normal	Normal	? old TB hip
7	NN	F	49	Pain in knees, about 4 years; grossly swollen knees.	Normal	Bilateral OA knees.	Normal	Not MJD
8	LN	F	28	Pain in hips, knees, ankles since before marriage	Epiphyseal dysplasia with OA.	Epiphyseal dysplasia with early OA	Normal	MJD +
9	MM	F	55	Pain in hips, knees, ankles for many years.	Bilateral gross OA.	Normal	Normal	MJD +
10	NN	F	45	Pain in hips, knees, ankles since birth of third child	Bilateral gross OA.	Normal	Normal	MJD +
11	GT	F	55	Aches in all joints for about 1 year. Walks normally	Normal	Normal	Old injury left 5th metacarpal	Not MJD
12	GM	M	75	Cannot walk far any more	Normal	Normal	Normal	Not MJD
13	SM	F	60	Normal on requestioning denies symptoms	Normal	Normal	Normal	Not MJD

TABLE XXXXV : SUBJECTS FROM SIBAYA SECTION 8 ENUMERATED AS HAVING MSELENI JOINT DISEASE

No.	Per-son	Sex	Age	History	Radio-graph hip.	Radio-graph knee.	Radio-graph hand.	Comment
14	FM	F	38	On requestioning denies symptoms.	Normal	Normal	Normal	Not MJD
15	MD	F	45	Pain in joints for many years. Classified MJD gait.	Gross bi-lateral OA	-	Carpal ab-normali-ties	MJD +
16	XM	F	43	Pains in legs for years.	Gross bi-lateral OA	Slight irregu-larity	Distal end of ulna slightly hypoplas-tic	MJD +
17	MQ	M 3	60 3	Unavailable for examinations by author.	Early OA	Normal	Normal	Possible MJD
18	MM	F	75	Died shortly after enumeration carried out. Not examined.				

INVESTIGATION INTO POSSIBLE LINKS WITH THE HIGH PREVALENCE AREA

Each person originally enumerated as having MJD was questioned as to place of birth, duration of domicile in the Sibaya area and relatives with possible MJD. The close relatives of those subjects assessed as probable cases of MJD were questioned and examined radiologically.

R E S U L T S

The age distribution of the inhabitants of Sibaya sections 7 and 8 were shown in Table II for females and Table IV for males. The number of adults (over 20 years) in section 7 totalled 141. Of these 13 (9,2%) claimed to have symptoms of joint pains and difficulty with walking. The number of adults in section 8 was 75, of which 5 (6,6% claimed to have symptoms of joint disease. (See Tables XXXXIV and XXXXV).

Two women, 13 and 14 , on requestioning, denied any symptoms, and both were found to be normal on X-ray. Respondent number 7 had symptoms referable only to the right hip joint which on X-ray was grossly destroyed - possibly on the basis of old T.B. One man aged 75, number 12 gave neither the typical history nor showed the typical gait of the MJD patient. The radiographs of his joints were normal and he could not be classified as MJD. Respondent 8 had grossly swollen and distorted knee joints which radiologically were affected by osteoarthritic changes but was otherwise normal. She too could not be classified as typical MJD. Respondent 1 and 12, though complaining of joint pains, had completely normal knee and

hand X-rays, and in the case of 12, a normal hip radiograph.

Patient number 1 had only minimal protrusio acetabulae. Both had a normal gait. Patient 18 was unavailable for examination by the author and could only be assessed radiologically. It is possible that he represents a case of MJD but the minimal changes of early osteoarthrosis in the hip joints are probably compatible with the signs of old age osteoarthrosis as he is about 75 years old. Since, in addition, his knees and hands are completely normal he probably does not have MJD.

Patient A (Subject 2):

Place of birth	:	Mseleni.
Lived in Sibaya	:	Since marriage.
Parents	:	Dead; MJD status unknown.
Siblings	:	One sister living in Sibaya has MJD (confirmed radiologically).
	:	One sister in Mseleni is unaffected (confirmed radiologically).
Husband	:	Dead, had no symptoms of MJD when alive.
Children	:	Daughter born in Sibaya - moved to Jozini on marriage - affected.
	:	Daughter (patient B) affected.
	:	Two sons left home to work in the towns. MJD status unknown.
Comment	:	A paternal uncle is the grandfather of one of the Mseleni dwarfs.

Patient B (Subject 3):

Place of birth	:	Sibaya.
Lived in Sibaya	:	All her life.
Parents	:	Mother affected (Patient A).
	:	Father dead: MJD status unknown.
Siblings	:	One sister - affected.
	:	Two brothers - unsure.
Husband	:	Unaffected (confirmed radiologically).
Children	:	Four children aged 6, 4, 2 and 1 years. The oldest was examined radiologically and appeared to be unaffected.

Patient C (Subject 4):

Place of birth	:	Sibaya.
Lived in Sibaya	:	All her life.
Parents	:	Dead: MJD status unknown.
Siblings	:	One brother said to be unaffected.
Husband	:	Said to be unaffected.
Children	:	Three died at birth: The only living daughter is an epileptic. Radiologically she is unaffected.

Patient D (Subject 5):

Place of birth	:	Sibaya.
Lived in Sibaya	:	All her life.
Parents	:	Dead. MJD status unknown. However, her maternal grandmother was said to have been affected and to have come from Manaba to Sibaya on marriage.

Siblings : One brother lives in Sibaya - affected (confirmed radiologically). He has four children under 6 years who were not examined.

: One sister lives in Sibaya - unaffected (confirmed radiologically), has two daughters, 16 and 20, who were examined radiologically and are normal.

Children : One daughter was unaffected on radiological examination, as were her two daughters aged 10 and 12 years.

: A second daughter was also unaffected.

Patient E (Subject 9):

Place of birth : Mseleni.

Lived in Sibaya : Since marriage.

Parents : Mother has MJD.

: Father: Dead, said to have been unaffected.

: Maternal grandmother dead: Said to have been affected.

Siblings : One brother is said to be affected.

: One brother is unaffected (confirmed radiologically).

Children : One died at birth, the other at 3 months.

Comment : This person is subject IV17 in Genealogy II - one of the Mseleni dwarfs is a first cousin to her, while 3 others are half first cousins of her mother, with a common paternal grandfather.

Patient F (Subject 10):

Place of birth : Malangeni.

Lived in Sibaya : Since marriage.

Parents : Mother was born in Sibaya, married at Malangeni - MJD status unknown.

: Father dead - MJD status unknown.

Siblings : Three brothers and one sister all in Malangeni - MJD status unknown.

Children : One son employed at Stanger - MJD status unknown.

: One daughter was unaffected on radiological examination.

Patient G (Subject 11):

Place of birth : Mseleni.

Lived in Sibaya : Since marriage.

Parents : Dead - mother said to have been affected.

Siblings : One sister now at Ophansi - said to be affected.

: Two brothers - MJD status unknown.

Children : Four children - girl of 8 and boy of 7 examined radiologically and appeared normal.

: Boy of 15 working in another area.

: Bou of four not examined.

Patient H (Subject 16):

Place of birth : Mbazwane.

Lived in Sibaya : Since marriage.

Parents : Mother died when subject was an infant.

: Father is dead and is said to have been unaffected.

Siblings : One sister has MJD.

: Four brothers are said to be normal.

Children : Two of her children were examined radiologically.

Both the boy of 12 and the girl of 9 were unaffected. Her oldest child is married at Mabibi and is said to be affected.

Patient I (Subject 17):

Place of birth : Maputa.

Lived in Sibaya : Since marriage.

Parents : Mother affected.

: Father dead, said to have been unaffected.

Siblings : One sister who is radiologically unaffected, and has an unaffected daughter of 15 and a son of 13.

: One brother was unavailable for examination.

Children : Her 12 and 8 year old sons were unaffected on radiological examination.

SUMMARY OF RESULTS

Prevalence rate: The final prevalence rates for Sibaya sections 7 and 8 including only the radiologically confirmed cases were 6, 4% and 5,8% respectively among the adult population, with an overall prevalence rate for the population of 3,4% and 2,6%

Age and sex: All 9 of the definitely affected people were women. The 10th person who was possibly a case of MJD was a man. Two of the women were in their twenties, three in their forties and four were over 50 years.

FAMILY HISTORY

Place of birth: Three were born in Sibaya and had lived there until the

present time. The others moved to Sibaya when they married men from the area; 3 from Mseleni; 1 from Malangani; 1 from Maputa; 1 from Mbazwana.

Parents: In 4 cases both parents were dead and the MJD status was unknown. The mother of one woman was available for examination as she lived elsewhere and the father of unknown MJD status, was dead.

The fathers of the remaining of women were dead and said to have been unaffected while the mothers of all 4 subjects were unaffected. In one case the maternal grandmother was also affected. One woman claimed that her maternal grandmother had been affected, though she was not sure of the MJD status of her parents.

Siblings: Six of the nine women had siblings with MJD, in two cases a brother and in five a sister. Two of these 6 pairs of sibs were born in Sibaya.

Children: One woman had 2 affected daughters, and another had 1 daughter who was said to be affected. One had no children and a fourth had 4 children all under 6 years. A fifth had 1 son of 4 and another unavailable for examination. Four women had one or 2 children each, who were radiologically unaffected.

D I S C U S S I O N

Sibaya sections 7 and 8 is a low prevalence area with an average prevalence rate of 3,6% as compared to the average prevalence for the Mseleni area of 18 % and for the Manaba area of 20 %

If an environmental factor is active in the affected area, it must presumably be an extremely potent agent to affect some 20% of the adult population. It appears that no such potent agent is active throughout the Sibaya area under investigation as the prevalence rate by comparison is very low, even among people who have lived in Sibaya all their lives. In fact, of the 9 cases found in Sibaya only three were born in the area and lived there during their formative years. The rest moved there on marriage by which time bone growth would have been completed. If one, therefore, considers the prevalence rate including only affected people who were born in Sibaya or resident there throughout the greater part of their period of bone growth and development, the prevalence rate for actual Sibaya cases drops to 0,9 %

The 3 Sibaya born cases are thus of some significance. Two of these women have a positive family history of MJD, with an affected parent or grandparent and an affected sib. This is highly indicative of a familial factor operative in the families of these people despite the fact that they are resident in an apparently nonendemic area for MJD. This factor could be heredity.

In at least one of the 3 Sibaya cases there is strong presumptive

evidence that a hereditary factor may be implicated, namely, the development of MJD in the 2 daughters (patient B) of an affected mother from Mseleni, despite the fact that the mother had moved to Sibaya on marriage and was living there throughout her pregnancy and at the time of the births of both the daughter and her sister.

The children of patient B are all under six years but further evidence of extreme interest may be gained by follow-up of these children to see if any of them develop joint disease. It is unfortunate that further family information was not available from the other 2 women born in Sibaya.

The fact that over half the affected women had at least 1 affected sibling is in keeping with the findings in Mseleni of a familial occurrence of the disease. However, of 9 children of the patients who were examined radiologically, only 1 was affected which is somewhat less than one would expect in a postulated condition of dominant inheritance.

Alternatively, this familial factor could come from the environment. Conceivably it could be something in their way of life which may result in intake of a noxious substance such as an unusual method of food preparation or storage. It would have to be a practice which these families indulge in as do the families of the high prevalence area but which is not seen in other families in Sibaya or in any other nearby area.

There is nothing to suggest that this may be the case but only a very intensive and detailed study of affected and unaffected families could exclude this possibility.

C O N C L U S I O N

This study has reaffirmed the familial nature of MJD and added additional evidence to the possibility of an genetic aetiology.

The findings however lead inevitably to a future in depth study of affected families in the control area. This will be discussed in greater detail in section X.

III.2.7 OTHER INVESTIGATIONS WHICH HAVE BEEN CARRIED OUT.

A STUDY OF SEROGENETIC MARKERS IN THE POPULATION.

Objectives:

1. To determine whether the people of the affected area, who were of mixed Tonga and Nguni descent now formed a homogeneous population..
2. To try to establish whether genetic drift could be responsible for the high prevalence of MJD in the population.
3. To determine whether two subgroups of the population i.e. affected and unaffected people could be distinguished on the basis of serogenetic markers.

Methods:

Blood samples were collected from a random sample of the adult population of the high prevalence area. Radiographs were taken of their hips, hands and knees. A fuller sample consisting of asymptomatic individuals was also tested as the number of unaffected people in the random sample was lower than that of the affected.

Results and conclusions

Detailed results together with the radiological will be published later as the data is still being analysed. However, two conclusions are already apparent.

1. The population appears to be a homogeneous random mating population with genetic markers in equilibrium in terms of Hardy-Weinberg Law[85b]
2. Since the gene frequencies conform to these reported by Jenkins[85a] for other South African Negro populations, it is probable that random

genetic drift cannot be implicated in the Mseleni situation.

FURTHER SPECIAL INVESTIGATIONS

Orthopaedic procedures were performed on four disabled female patients from Mseleni, with resultant pain relief and improvement in joint function. These procedures will form the basis of a future report by colleagues and will not be discussed here in any detail.

However, during the period of hospitalization, it was possible to carry out biochemical and serological tests and histological studies were performed on the bone specimens obtained at operation. These investigations were carried out by colleagues from various institutions (see acknowledgements) and will only briefly be mentioned here to complete the description of the Mseleni studies to date.

Biochemical studies included analysis of the following parameters in the blood and urine:

1. Total serum protein and electrophoresis.
2. Immunoglobulins.
3. Bilirubin, thymol turbidity and floculation tests.
4. Uric acid and creatinine.
5. Calcium and phosphorus excretion.
6. Serum calcium, phosphorus, copper, magnesium, iron.
   Iron binding capacity.
   Caeruloplasmin and transferrin.
7. Hydroxy proline excretion.
8. Plasma 11-hydroxy corticosteroids.
9. Acid and alkaline phosphatases.
   Serum glutamic oxalo acetic transaminase.

No significant abnormalities were found. Specifically calcium, phosphorus and alkaline phosphatases were normal. Routine radiological tests revealed no abnormalities. Serological tests included Wassermann test, brucella agglutination test, rheumatoid arthritis latex agglutination test, a test for anti-nuclear factor and the chlamydia group antigen complement fixation test. One patient had positive Wassermann and Reiter complement fixation tests. Two of the four had a positive (1 in 64) reaction to the chlamydia test. The remaining tests were negative.

Histology

Femoral head specimens obtained as a result of bilateral hip arthroplasties on 3 of these patients were studied histologically by colleagues. Non specific changes of a low grade chronic inflammatory process were seen in specimens from two of the patients, while the tissues from all three demonstrated alterations indistinguishable from the changes of degenerative joint disease.

No definite aetiological reason for those chronic, low grade inflammatory changes was seen.

These specimens were obtained from elderly patients with marked secondary degenerative changes in the joints. It is obvious that ideally histological studies of Mseleni Joint Disease should be carried out on bone biopsy specimens from younger patients with the early stage of the disease. This has not been possible to date.

TWIN STUDIES

Further evidence to support or reject the hypothesis of a genetic aetiology will be obtained from Twin Studies. Approximately thirty pairs of twins have been identified in the high prevalence and control areas. Radiological examination of those not already examined is in progress. Serogenetic studies on twins of like sex will be carried out where necessary to establish whether they are monozygous or dizygous.

The radiographs will be studied to determine whether the subjects are affected or not and if the degree and distribution of lesions are similar. Information regarding upbringing will be sought to determine if twins were separated at an early age, or have been brought up together.

The findings may be interpreted as indicated by Carter[34]. If monozygotic co-twins are no more often affected than are the like-sex dizygous twins, it is probable that influence of genetic factors is not great.

If monozygotic co-twins are almost always affected but like-sex dizygous twins less so it is probable that the disease is largely determined by genetic factors.

If the monozygotic co-twins are not always affected but are substantially more often affected then the like-sex dizygous twin it is probable that both genetic and environmental factors are important in the disease aetiology.

SUMMARY OF THE CHARACTERISTICS OF MSELENI JOINT DISEASE

The prevalence of the disease

The overall high prevalence rate for MJD in Mseleni, Manaba (2 & 3), and Mbazwana (2 & 3) was confirmed and Sibaya 7 and 8 selected as a control area.

Radiological prevalence rates

Radiological prevalence rates based on the presence of dysplasia or osteoarthritis in the hip joint (which is affected in all but isolated cases) indicate that about 16% of the men and 46% of the women have MJD.

Familial aspect of MJD

There is a strong familial element to the disease. Most affected individuals have several affected first degree relatives.

Within a kraal vertical transmission of the disease may be seen through three to four generations. Whether the apparent horizontal transmission among the adult women of a kraal is a genuine phenomenon or a spurious effect has not been established. Extensive pedigrees reveal a pattern of occurrence compatible with inheritance of an autosomal dominant gene of high penetrance.

Clinical features

Onset of the disease: There is no obvious abnormality detectable in the newborn, or very young child. The earliest indication of disease may be slight swelling of the knees, or pain and rapid tiring on exertion. This may appear from about 6 years onward. However, the majority of patients claim to have been perfectly asymptomatic till their thirties.

thirties, when increasing pain and stiffness of the legs become apparent. Many women relate the onset of symptoms to the time shortly after the birth of their children.

Pain is most commonly experienced first in the ankle joint, then the hip, and then the knee. The development of pain and disability is gradual and unrelated to an acute illness.

Symptoms

The only symptoms are those referable to the skeletal system. The lower limb joints, hips, knees and ankles are most commonly the site of pain while occasionally the hands, feet, shoulders or back are painful.

Disability

While for the younger patients pain and stiffness on walking are the main problems, the majority of older people require sticks or crutches to aid their movements. In very few cases is the crippling so severe that the patient can no longer walk.

However, the disease is so much a way of life among the people of Mseleni and Manaba that even severely dwarfed and disabled women marry and produce children though delivery is by Caesarian section.

Clinical stigmata

The appearance of an affected child may be completely normal, some however, may show slightly enlarged knee joints, mild to moderate genu varus or valgum, and a slightly waddling gait.

Affected adults have a characteristic waddling gait which in the older patient becomes slow, stiff-hipped and shuffling. The patient is bent forward at the hips and usually leans heavily on one or two sticks. Marked lumbar lordosis and genu valgum is common.

There is no specific abnormality of the skull, hair, facies and nails.

Height

A range of heights is seen in the parents with MJD. Affected women were found on the average to be slightly shorter than our unaffected group of women. Thirty-nine adult dwarfs were found.

Examination of systems other than the skeletal system

No consistent abnormalities were found in any other systems and no evidence of a generalised systemic distribution was found.

Skeletal system

Many of the younger children who were asymptomatic yet had radiological evidence of the disease were normal on examination.

The earliest abnormality detected was a mild flexion contracture or a decreased ranged of flexion or internal rotation. The findings in the older patients were those of degenerative arthrosis. Contractures, decreased range of movement and crepitus were predominant features. Some of the older patients had pronounced Heberden's nodes.

Radiological findings

MJD is characterised by a wide spectrum of stigmata. A variation in form and severity of lesions in each type of joint, and differing combinations of affected joints were prominent features. Spinal involvement was variable, ranging from absent to severe deformities and platyspondyly. The dwarfs manifested the most severe degree of the disease.

It is apparent that while certain patients would unequivocably be classified as spondylo-epiphyseal dysplasia, equally, others would be classed with the multiple epiphyseal dysplasias. It appears that there is much overlap in this population : MJD cannot therefore be placed solely into either category.

Since it was apparent from clinical and radiological studies that MJD phenotypically may be classified with the multiple epiphyseal dysplasia and spondylo-epiphyseal dysplasia group of disorders, the literature on these hereditary bone dysplasias was reviewed in order to define the relationship of MJD to these disorders and to determine whether MJD could be classed into any of the subgroups of these conditions.

SECTION IV

A REVIEW OF THE LITERATURE

ON THE HEREDITARY EPIPHYSEAL

DYSPLASIAS

CONSTITUTIONAL DISORDERS OF BONE

In 1935, when Brailsford[23] published his "Dystrophies of the Skeleton" he could subdivide the conditions grouped together under the heading "Chondrodysplasia" into only ten major groups. Amongst these were achondroplasia, a group which he termed chondro-osteodystrophy, and the others which he classed together as"unclassified dystrophies". Conditions such as multiple dysplasia had not yet been defined.

In the same year, Fairbank[54], in a review of general affections of the skeleton, first suggested that cases with multiple epiphyseal abnormalities should be classified into two groups. The first consisted of cases often published under the title of "multiple osteochondritis" which he felt were often developmental errors, and not strictly comparable to osteochondritis as seen, for example, in the knee. This condition he considered to be an inherited affection of the skeleton, for which he later suggested the name "Dysplasia Epiphysealis Multiplex".

The second class with epiphyseal abnormalities he considered could be readily distinguished from the first group. Within this group he classified cases into several types, one of which was Morquio-Brailsford disease. These conditions fitted chondro-osteodysplasias.

Sixteen years later when Fairbank[56] published his "Atlas of General Affections of the Skeleton", conditions such as Dysplasia Epiphysialis Multiplex, Dysplasia Epiphysialis Punctata and Metaphyseal Dysostosis had been differentiated from the "unclassified dystrophy group" of Brailsford but the biochemical abnormalities of the mucopolysacchari-

doses had not yet been discovered, and Fairbank could state in the chapter on achondroplasia that the only condition likely to simulate this condition at birth is osteogenesis imperfecta.

In 1964, Rubin[152] propounded his "Dynamic Classification of Bone Dysplasias" in which he suggested that at each specific region of bone growth a particular intrinsic error of development operative at a particular time will produce a specific type of anomaly. He classified the bone dysplasias by site (epiphyseal, physeal, metaphyseal and diaphyseal) by type of growth (hyperplasia or hypoplasia), by the specific error involved (e.g. failure of articular cartilage etc.), and the the time that the abnormality is detectable (congenita - present at birth, tarda - noticed later in life).

By 1971, a mere 36 years after Brailsford, a meeting of paediatric radiologists was held in Paris to formulate a workable nomenclature for constitutional or intrinsic diseases of bones.[53] Those constitutional diseases of bone with unknown pathogenesis were classified into 2 main groups. These were the Osteochondrodysplasias (abnormalities of cartilage and/or bone growth and development) and the Dysostoses (malformation of individual bones singly or in combination). These two groups which include 7 of the groups of Brailsford's classification are now subdivided into some 89 distinctive conditions, many of which can be further subdivided into specific forms on a basis of varying modes of inheritance. Brailsford's chondro-osteodystrophy Group A is now included with the diseases due to an abnormality of mucopolysaccharide metabolism, while the differential diagnosis of achondroplasia in the new-born

covers some 15 conditions. While it realised that the Paris classification will need to be updated as other conditions are defined, for the present it is the currently accepted nomenclature.

Thus, it can be seen that the field of knowledge of skeletal dysplasias has expanded enormously in the last fifty years and of necessity, this review of the literature will be restricted to those conditions which have been considered as the possible cause of Mseleni Joint Disease. These are the group of conditions called Multiple Epiphyseal Dysplasia, and the various forms of Spondylo-epiphyseal dysplasia.

THE HEREDITARY EPIPHYSEAL DYSPLASIAS

The disorders which have now came to be known as the multiple epiphyseal dysplasias and the spondylo-epiphyseal dysplasias have long been characterised in the literature by a multiplicity of names and confused diagnoses.

A brief history of the early literature on Dysplasia Epiphysialis Multiplex and the Spondylo-epiphysialis Dysplasias will be given, and then the present concepts and classification of these disorders will be presented.

Dysplasia Epiphysialis Multiplex

The first recorded cases in the English literature, usually cited, are those of Barrington-Ward[13] in 1912 - published as a case of "double coxa vara with other deformities occurring in a brother and sister", but it is possible that the four cases described by Drysdale and Herringham[46] in 1908 as "an undescribed condition of dwarfism associated with a spatulate condition of the hands" were actually cases of multiple epiphyseal dysplasia.

In 1935 Fairbank[54] described a man, markedly below average height, with short broad, square fingers and toes, who showed the appearance of bilateral pseudocoxalgia at 14 years of age, and was later shown to have similar changes at the upper end of the humerus. This condition, he felt was probably an inherited affection of the skeleton, and he classified it with a group of cases he was later to call dysplasia epiphysialis multiplex.

Fairbank[55], in 1947, finally delineated the features of the condition basing his description on 20 cases and established dysplasia epiphysealis multiplex as a clinical entity. He defined the condition as "a developmental error resulting from some unknown cause, characterised by dwarfism, stubby digits and mottling or irregularity in density and outline of several of the developing epiphyses".

He defined the features of the condition as follows:

1. An affection of children and young people.
2. Affects both sexes.
3. As a rule it is not inherited or familial.
4. Intelligence is usually normal.
5. Presenting symptoms are difficulty on walking, or pain and stiffness of the hips.
6. Short limbed dwarfism is the rule.
7. The hands are short, stubby with blunt ends although the relative lengths of the digits are normal.
8. Some epiphyseal enlargement may be seen.
9. The spine is usually normal in length and ossification.
10. Blood examinations have revealed nothing abnormal.

The radiological findings were described in detail. The outstanding feature was irregularity in density and shapes of multiple epiphyseal ossification centres resulting in a permanently deformed and irregular epiphysis. The joints said to be commonly affected were hips, shoulders, ankles, then knees.

Fairbank[55] described seven conditions to be considered in the differential diagnosis of irregular epiphyseal ossification. These included cretinism, dysplasia epiphysialis punctata, Morquio-Brailsford, osteochondrodystrophy, dyschondroplasia, osteopoikilosis, osteopetrosis and pituitary gigantism.

From Barrington-Ward's[13] (1908) publication until the present time, numerous case reports and reviews on the multiple epiphyseal dysplasias have been published. These have been surveyed in Table XXXXVI

The Spondylo-epiphyseal Dysplasias (SED)

The early literature on the spondylo-epiphyseal dysplasias is confused by the classification of a wide variety of cases under the name of Morquio's Disease. In 1929, Morquio[132] of Uruguay and Brailsford [22] of England independently defined a specific disorder characterised by marked dwarfism with onset in the second or third year of life. The clinical picture is diagnostic with short barrel chest, pigeon breast, dorsal kyphosis, short neck and characteristic facies. This condition became known by such names as Morquio's Disease, or Morquio-Brailsford Disease or chondro-osteodystrophy. Numerous instances of typical or atypical cases were described under these titles over the next forty years.

In 1952, Brante[26] discovered dermatan sulphate (Chondroitin sulphate B) in the liver of 2 patients with the Hurler syndrome and suggested the term mucopolysaccharidosis for the disorders caused by defects in mucopolysaccharide metabolism. In 1957, Dorfman and Lorincz[45] found that urinary excretion of acid mucopolysaccharides was increased in the Hurler syndrome.

Zellweger et al.[184] and Maroteaux and Lamy,[118], in 1961, described abnormal elimination of mucopolysaccharides in Morquio's disease. This abnormal elimination of keratin sulphate (kerato-sulphate) established the entity of Morquio's disease as a mucopolysaccharidosis and it is now known as MPS IV[53].

It became evident that a number of different conditions had been classified together as so-called Morquio's disease and gradually these disorders were differentiated into separate entities.

X-linked SED tarda is a clearly delineated syndrome in which short trunk dwarfism is transmitted as an X-linked recessive trait. Maroteaux et al.[116] (1957) described three pedigrees and proposed the name "dysplasia spondylo-epiphyseal tardive".

Pseudo-achondroplastic spondylo-epiphyseal dysplasia (PsA-SED) was first delineated by Maroteaux and Lamy[117] in 1959, although cases had previously been described as achondroplasia. The disorder is often mislabelled achondroplasia because both are characterised by rhizomelic limb shortening with relatively long trunk. However, PsA-SED is not obvious at birth and the skull and facies are normal.

Numerous case reports of the spondylo-epiphyseal dysplasias, many of which were published incorrectly under the title of Morquio's Disease, are included with the multiple epiphyseal dysplasias in Table XXXXVI.

TABLE XXXXVI : SURVEY OF REPORTED CASES OF HEREDITARY EPIPHYSEAL DYSPLASIA

(See reference number of article in lower left hand corner of the second column).

No.	Authors	Year	Cases	Possible inheritance	Spinal Abnormalities	Positive special investigation	Comment	Classification
1	Drysdale and Herringham 46	1908	3 sisters with clinically normal parents and three brothers. Woman of 30	Possible A.R.	Not stated	Nil	Possible cases of MED. Insufficient detail to decide.	Possible MED
2	Barrington-Ward L.E. 13	1912	Brother and sister	?	Not stated	Nil	The first clear cases of MED in the English literature.	MED
3	White, J.R. 178	1924	Boy of 11	?	Not stated	Nil	Presented as achondroplasia - appearance atypical	PsA MED/ SED
4	Buxton, St. J.D. 30	1930	Boy 20, 4 apparently normal sibs.	?	Not stated	Urine normal	Presented as dwarf with stippled epiphyses.	MED
5	Warkany, J. and Mitchell A.G. 173a	1934	12 year old boy. 6 sibs and parents asymptomatic for joint disease.	?	Irregularity of a few vertebrae. No flattening.	Mild anemia.	Probable MED	MED

TABLE (Continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Positive special investigation	Comment	Classification
6	Fairbank, H.A.T. 54	1935	Male of 27	?	Not stated	Nil	Probable MED first suggestion that the epiphysial errors like the osteochondritides may be a district group.	MED
7	Campbell Golding, F. 32	1935	3 children in family of 6. Parents were cousins. Sibs of 35 and 26 years. Unrelated parents clinically normal.	? AR ? AR	Flattened vertebral bodies	Nil	Descriptions not clear for each patient but probably a form of SED. Author considered cases to be mild forms of Morquio's.	SED Tarda.
8	Hirsch, I.S. 71	1937	Woman of 59 three sons, and a daughter. Two brothers with two normal brothers and a normal sister	Autosomal dominant. ? AR	Flattened wide vertebral bodies. Thoracic wedging causing kyphosis	Nil	Not the typical facial or bodily appearance of an MPS IV patient. suggested a new classification.	SED
9	Gardiner - Hill, H. 63	1937	-	-	-	-	Reviewed disorders for growth and development.	Varied

TABLE (Continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Positive special investigation	Comment	Classification
10	Engel, A. 51	1938	Female 44	?	Slight flattening of vertebrae with irregular surfaces arthritic changes.	Nil	Authors' differential diagnosis between juvenile Rheum. Arthritis and hereditary epiphyseal dysplasia.	MED or SED. Tarda possible
11	Cockayne, E.A. and Yarrow, D.E. 182	1938	Boy of 7 years. Parents and 2 Sibs clinically normal.	?	Irregularity	Nil Calcium, phosphorus and alkaline phosphatase normal.	Generalised deformed and stippled epiphyses.	MED
12	Wiles, P. 180	1938	Female 6 years	?	Not stated	Nil	Bilateral symmetrical generalised changes like osteochondritis.	MED
13	Jacobsen, A.W. 84	1939	4 out of 20 affected members in 5 generations of one family, all males.	X-linked Recessive	Flattening, irregularty with sunfish appearance in the younger cases. Rigid spines.	Nil	Clearly evident X-linkage pattern.	X-linked SED Tarda

TABLE (Continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Positive special investigation	Comment	Classification
14	Romanus, R. 150	1940	Boy of 9, 3 brothers, their sister and a nephew of 9.	Sporadic	Platyspondyly with kyphosis.	Nil	Generalised epiphyseal disturbance. Not MPS IV.	SED
15	Shafar, J. 157	1941	2 sisters. 3rd sister, mother and grandmother said to be affected.	Probable A.D.	Normal	Nil	Discusses classification of brachydactyly	MED
16	Halberstaedter, M. 66	1943	Brothers of 35 and 39. Sister radiologically normal. Brother and parents normal on history.	Recessive. ? X-linked.	Platyspondyly with central humping. Spinal rigidity scoliosis.	Nil	Predominantly spinal lesions with pelvic abnormality and mild changes in the hand.	SED
17	Resnick, E. 146	1943	Mother and her identical male twins.	Autosomal dominant	Not specified	Nil	Multiple osteochondritis-like changes.	MED

TABLE (continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Positive special investigation	Comment	Classification
18	Brailsford, J.F.	1946	2 Brothers; 2 sisters the father and mother normal.	Nil	Nil	Nil	Hips and hands only affected	MED
19.	Fairbank, H.A.T.	1947	Reviewed 20 cases, 12 males and 9 females including father/son, 2 brothers 2 sisters.	Familial in 6 cases	Normal in all but one case.	Nil	Defined MED as distinct condition. Includes one case of metaphyseal dysostosis	MED

TABLE (Continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Possitive special investigation	Comment	Classification
20	Baastrup, C.J. 5	1948	Boy 7. Parents 2 Sibs clinically normal.	Sporadic	Irregularity of vertebral bodies in lumbar region.	Nil	Tall. Normal hip joints. Knees, elbows, carpus, tarsus, metatarsus affected.	MED
21	Ellman, P. 48	1949	Son of normal parents who were first cousins. Girl of 16, parents first cousins	Recessive	Platyspondyly with irregularity of the vertebral body. Kyphosis	Serum calcium slightly low.	SED with marked spinal deformities but not true Marquio's. Discusses difference from Rheumatoid arthritis.	SED
22	Scott, L.G. 155	1952	Male of 8 years.	?	Not mentioned	Nil	Brief report	MED.
23	Waugh, W. 174	1952	3 sisters of 8 sibs. Father chronic Rheumatoid arthritis.	Possible Autosomal dominant	One case had slightly flattened lumbar vertebrae.	Nil	All 3 had cleft palates.	MED.

TABLE (Continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Positive special investigation	Comment	Classification
24	Watt, J.K. 172	1952	Brother and sister and 2 other females.	No family studies done.	Normal	Nil	Typical cases.	MED.
25	Jackson, et al. 81	1954	Males of 22 and 10. Daughter two sons and the mother.	? sporadic Possible dominant.	Midthoracic flattening and irregularity of vertebral bodies in two cases.	Nil	Emphasizes lack of disability in the adults. Good differential diagnosis.	MED
26	Ribbing, S. 147	1955	Family with MED. Girl with osteochondritis	Autosomal recessive ?	Moderate thoracic Kyphosis	Nil	Discusses relationship between osteochondritis and epiphyseal dysplasia.	MED
27	Maudsley, R. H. 123	1955	10 out of 17 people in 3 generations of 1 family. Brother and sister. Father and son.	Autosomal dominant. ? Autosomal dominant	Irregularity flattening or wedging in some cases.	Nil	Premature OA	MED

TABLE (Continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Positive special investigation	Comment	Classification
28	Christensen, W.R. et al. 35	1955	Mother and 2 daughters. Boy of 5.	Autosomal dominant.	Normal		Pedigree shows 9 affected members of 14 F and 7 males but based on history not radiology.	MED
29	Shephard, E 158	1956	Boy of 14, his mother and grandmother with 3 other possible cases.	Autosomal dominant.	Boy: T11 irregular grandmother large osteophytes.	Nil	Described depressions in bones sometimes with bone islands. cf.Ribbing	MED
30	Cope, et al 38	1956	Male of 10 years. Parents and 8 sibs clinically well.	Apparent sporadic	Normal	Raised alkaline phosphatase.	First reported case in South African Negro.	MED

TABLE (Continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Pos. special investigation	Comment	Classification
31	Levy et al 106	1957	Twin boy 6 yrs.	Sporadic	Normal	Slightly raised alkaline phophatase 16.1 units (3.5 to 13 units) normal for laboratory ca^{++}, P; normal. Increased I 131 uptake - not explained.	Only one of binovular twins affected.	MED
32	Freiberger, R.H. 61	1958	Boy of 6, parents and sister normal. Girl of 9 family normal. Boy of 11 parents and two sisters short but normal.	Sporadic Sporadic Sporadic	Normal Normal Irregularity of vertebral bodies with anterior wedging. Natural disc space.	Nil	Emphasises short stature and good prognosis re disability of MED.	MED MED MED

TABLE (Continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Positive special investigation	Comment	Classification.
33	Barrie, H. et al. 12	1958	9 people in 3 generations of 1 family. 5 cases in 2 generations of a 2nd family. Father and son.	Autosomal dominant	Slight flattening and Scheuermann's type changes in one child.	Nil	Suggested that physiotherapy relieved symptoms and lessened resultant disability.	MED
34	Litchman and Chirls 108	1958	4 brothers 2 of whom were twins, with sister possibly affected. Father and son. One male, 2 normal sibs.	Uncertain Autosomal dominant. Uncertain	Platyspondyly with moderate wedging and kyphosis. Irregular articular margin. One had lumbar hemivertebra.	Nil	The authors considered these cases to be MED but the platyspondyly would tend to place them in the SED group.	MED / SED

TABLE (Continued)

No	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Positive special investigation	Comment	Classification
35	Schwartz, S. 153	1959	Adult male	Uncertain	Flattened with irregular outline.	Routine tests normal	Presented at 30 years with pains in back and feet.	SED
36	Weinberg, et al 175	1960	45 affected out of 107 members in 6 generations of a family.	Autosomal dominance	A few had mild irregularity of the vertebrae. Otherwise normal.	Routine tests all normal.	Extensive pedigree of autosomal dominant pattern.	MED
37	Barber, H.S. 11	1960	4 affected brothers out of 7 males and 2 female sibs. Parents appeared normal.	Possible X-linked recessive.	Flattened irregular vertebrae with narrowed and sometimes obliterated disc space in lumbar region. "Fish mouth" appearance lumbar spine	Nil	Only spine and hips affected. Possible tarda forms of X-linked recessive SED.	SED

TABLE (Continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Positive special investigation	Comment	Classification
38	Rowatt-Brown and Rose. 151	1960	Family with 16 affected people in 6 generations.	Possible autosomal dominant	Irregularity of vertebrae. Slight flattening.	Tests negative including Rose-Waaler Latex; mucopopolysaccharidoses, homogentisic acid and alkaline phosphotase.	One affected boy has a mother with symptoms but no radiological abnormality except intervertebral calcification.	MED/ SED
39	Leeds, N. E. 104	1960	Father and son.	Autosomal dominant	Normal	Nil	Emphasized that early physiotherapy can lessen later disability.	MED
40	Ford et al 59	1961	Son and daughter of a "circus dwarf".	Probable autosomal dominant	Flattened slightly biconvex vertebrae. Anterior breaking in lumbar region.	Tests negative including alkaline phosphatase.	Girl developed paraplegia after mild trauma.	PsA SED

TABLE (Continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Positive special investigation	Comment	Classification
40	Ford et al. (Contd) 59	1961	Daughter of healthy parents with two normal brothers.	Uncertain	Vertebral irregularity but no flattening.	Routine tests normal.	Mother attempted abortion in second month with quinine. The authors questioned possibility of a "phenocopy" of the hereditary dysplasias.	PsA MED
41	Munk and Boldo 134	1961	12 year old boy. Parents and 1 sister normal.	Probably sporadic	Normal	Routine tests normal	Case report with brief description of MED and differential diagnosis.	MED
42	Tempany, E. 168	1961	Girl of 15. Father in mental home, mother related and has cleft palate. Brother low IQ.	Uncertain	Not specified.	Urine amino acid. shows raised glycine ornithine, trace of asparagine. IQ 30 Abnormal glucose tolerance test.	Associated mental retardation and diabetes millitus. Mother had cleft palate. cf Waugh's cases.	MED

TABLE (Continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Positive special investigation	Comment	Classification
43	Klenerman, L. 92	1961	Adult male. Parents first cousins. Two of 6 siblings also short .	Possible autosomal recessive.	Platyspondyly with narrowed disc spaces.	Nil	Multiple loose bodies removed from hips and elbow.	SED
44	Hobaek, A. 73	1961	Families 11 - 38	Varied from dominant to recessive.	Varied	Nil	A review of hereditary chondrodysplasias in 43 Norwegian families.	Varied
	Anderson et al. 3	1962	7 children with MED or SED	Varied	Varied	Histological findings presented.	Histological study of epiphyseal cartilage.	MED/ SED
46	Monty, C.P. 131	1962	5 people in three generations.	Uncertain	Normal	Nil	Hips only affected in 2 cases. In one the ankles and hands affected. Author called this familial Perthe's disease.	? MED Type II

TABLE (Continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Positive special investigation	Comment	Classification
47	Moldawer et al. 130	1962	Adult man, his brother and his son. Man, his mother, brother, sister, nephew and niece.	Autosomal dominant. Autosomal dominant.	Platyspondyly. Platyspondyly with vertebral wedging.	Nil	Emphasises that osteochondrodystrophy may present for the first time with degenerative joint changes masking the dysplasia.	SED
48	Hodkinson, H.M. 75	1962	3 cases among 8 living sibs with a father with osteoarthrosis.	Probable autosomal dominant.	Not stated - probably normal.	Normal including serum calcium phosphorus and alkaline phosphatase.	All 3 had bilateral bipartite or double layer patellae.	MED
49	Cowan, D.J. 40	1963	6 cases in 5 generations. A further possible 6 cases not examined.	Autosomal dominant.	Affected in 1 case.	Nil	Several asymptomatic people with marked radiological abnormalities.	MED

TABLE (Continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Positive special investigation	Comment	Classification
50	Langer, L.O. 101	1964	Two brothers, 47 and 39. First cousins (of Jacobsens original family) aged 42, 25.	X-linked recessive.	Platyspondyly with humping up of bone in the central and posterior portion of inferior and superior aspect of vertebral bodies.	Normal including phosphatases, and mucopolysaccharide studies and homogentosis and in urine.	Emphased humped vertebral changes in lumbar spine as diagnostic of SEDT.	SEDT
51	Poker et al 144	1965	2 pairs of brothers aged 14, 11, 8 and 6 years.	X-linked recessive.	Generalised platyspondyly anterior narrowing on lateral view with humping of dense bone posteriorly.	Normal including mucopolysaccharides and karyotype.	Reviewed the literature on platyspondyly.	SEDT

TABLE : (Continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Positive special investigation	Comment	Classification
52	Berg. P.K. 18	1966	Woman of 39 and her sons of 11 and 8 years. 5 year old boy.	Possible autosomal dominant unsure recessive	Normal Normal	Normal serum calcium phosphorus, alkaline phosphatases.	Only knees affected in the mother but multiple joints in the sons.	MED Possible MED
53	Kozlowski and Budzinska 95	1966	Boy of 7. Parents and sibs healthy. Girl of 12 Parents unaffected	Apparently sporadic. Apparently sporadic	Flattened irregular and T.L. were hypoplastic. Slight flattening and irregularity	Normal routine tests and serum calcium, phosphate, phosphatase mucopolysac	Called metaepiphyseal and epimetaphyseal dysostosis by the authors A form of dysplasia epiphyseal multiplex	MED
54	Kozlowski and Lipska 96	1967	8 cases in 2, generations of family.	Autosomal dominant	Only 1 had spinal involvement fragmented annular ossification.	Nil	Emphasized intrageneration resemblance of affection. Cases from the European literature discussed.	MED

TABLE (Continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Positive special investigation	Comment	Classification
55	Bachman, R.K. 6	1967	Woman of 47 her son, 7, and daughter 10.	Probable autosomal dominant.	Not specified.	Normal, including serum phosphatases urine, amino acids, Ca phosphate and karyotype.	Generalised epiphyseal dysplasia in the children with severe OA, hips in the mother, hands in children strikingly abnormal.	MED
56	Lindseth et al 107	1967	Boy of 8, parents and 5 siblings normal on radiological examination.	Sporadic	Marked platyspondyly with irregularity of the bone plates.	Normal routine tests. Karyotype: Deletion of short arms of a G-group chromosome in patient and mother.	Histological study of iliac crest biopsy specimens. Discussion of significances of chromosomal aberration.	Ps Ach SED

TABLE (Continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Positive special investigation	Comment	Classification
57	Hunt et al [79]	1967	Brothers of 12 and 4. Sister said to be normal. Parents normal.	Unsure	Flattening and slight biconcavity of the vertebral bodies.	No abnormal urinary mucopolysaccharides	Histological and biochemical analysis of epiphyseal plate cartilage in one case. Associated slipped capital femoral epiphysis in both, osteosarcoma in one.	MED
58	Weinfeld et al [176]	1967	1 of two possibly affected brothers with 5 other normal sibs and normal parents. 3 brothers (two of whom were twins) of 5 probably affected brothers with 2 normal sisters.	Possible X-linked recessive. Probable X-linked recessive.	Platyspondyly with posterior humping of vertebral bodies.	Nil reported	Stressed the frequent presentation of SEDT as premature OA of a weight bearing joint.	SEDT

TABLE (Continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Positive special investigation	Comment	Classification
59	Hoefnagel et al 76	1967	12 cases in two generations of a family	Autosomal dominant	Affected in 3 - abnormality not specified.	No consistent abnormality in blood or urine.	Excluded close linkage of the disorder with the Kell and MNS loci. Hip normal in 8 of the 12 cases.	MED
60	Jacobs, P.A.	1968	8 cases in 3 generations	Autosomal dominant	Not specified	Nil	States that osteotomy may prevent degenerative changes and relieves them when they occur later.	MED
61	Juberg and Holt 86	1968	4 affected people in a sibship of 15 with normal parents.	Possible autosomal recessive	Slight flattening of vertebral bodies.	Normal including serum calcium, phosphorus, alkaline phosphatase urinary amino acids and karyotype.	Double patellae in 3 cases. The 4th had had bilateral patellechomy. Presents evidence for recessive inheritance of MED.	MED

TABLE (Continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Positive special investigation	Comment	Classification
62	Specht, E.E. 165	1968	29 year old male, parents, 2 sisters, one brother, normal height and body configuration.	Possible sporadic, X-linked recessive or autosomal recessive.	Irregularity of vertebral end plates. Biconvex configuration in A-P projection with narrow disc space.	Normal, including alkaline phosphatase and urinary homogentisic acid.	Presented with severe back pain.	SEDT
63	Hulvey and Keats 78	1969	5 cases of 19 probably affected people in 6 generations.	Autosomal dominant	One had minor irregularity of end plates in lower thoracic region.	Routine tests normal	Discusses lack of correlation between spinal involvement and severity of peripheral joint abnormality.	MED
64	Felman, A.H. 58	1969	2 children of a very short father and normal mother.	Unsure	Marked lumbar lordosis with dorsal kyphoscoliosis extensive irregularly fragmentation and anterior wedging of thoracolumbar vertebrae.	Normal, including alkaline phosphatase and urine mucopolysaccarides	MED with very severe spinal changes but not generalised platyspondyly.	MED

TABLE (Continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Positive special investigation	Comment	Classification
65	Mansoor [114]	1970	Father and 2 sons 5 other cases not all typical MED.	Autosomal dominant Varied	Not affected Not stated in all.	Nil	Two cases with retardation and congenital cataracts and two cases with abnormalities only in feet are not typical MED.	MED
66	Diamond, L. [43]	1970	31 cases in 4 generations were seen.	Autosomal dominant but greater than expected frequency of cases.	Varied from irregularity, Schmorl modes with anterior wedging to platyspondyly with posterior humping and anterior tonging or beaking.	Extensive studies on blood and urine were negative. Large fragile chromosome. 16 in 5 karyotypes 9 karyotypes normal.	Distinguishes a "forme fruste" with minimal changes. Found cases with typical MED and typical SED spinal changes in this one family.	MED/ SED

TABLE (Continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Positive special investigation	Comment	Classification
67	Bannerman [10]	1971	Restudied and extended Jacobsen's original pedigree.	X-linked recessive.	Typical appearance of vertebral bodies.	Linkage studies for colour-blindness and blood groups were negative.	Studied heterozygens female carriers.	SEDT
68	Kozlowski et al	1972	Boy of 13.	Recessive	Generalised platyspondylysis with irregularity of the vertebral bodies.	Normal including Ca, P, alkaline phosphatase and urine mucopolysaccarides.	Skull abnormalities includes platybasia were present. Associated mental retardation. Hearing loss.	SED
69	Kozlowski et al [97]	1972	11 year old boy	Recessive	Spotty calcification of vertebral rings.	Nil	Macroepiphyses in peripheral skeleton.	SED

TABLE (Continued)

No.	Authors	Year	Cases	Possible inheritance	Spinal abnormalities	Positive special investigation	Comment	Classification
70	Murphy et al [135]	1973	24 affected people in 6 generations of a family.	Autosomal dominant with complete penetrance	Affected in 4 of 17 patients examined. Minor changes.	Serum calcium, phosphorus and phosphatase normal.	Parathesias, paraplegias, unusual dermatoglyphic patterns. Osteochondritis disscans and Blount-Barber disease noted in 1 or more family members.	MED
71	Harper, P.S. et al [69]	1973	3 brothers with 2 brothers and 2 sisters unaffected. Adult male	Probable X-linked recessive. Apparently sporadic.	Yes	Tests normal - including urinary mucopolysaccharides		SEDT

Current classifications of the Hereditary Epiphyseal Dysplasias

In 1969, Maroteaux [115] defined the Spondylo-epiphyseal Dysplasias as "those abnormalities of bony growth selectively affecting the vertebra, carpal and tarsal bones, epiphyses of the long bones and sometimes, the neighbouring metaphyses". He categorised the conditions in three groups, the multiple epiphyseal dysplasias; included disorders where changes in the long bones are limited to the epiphyses while the spinal lesions affect the vertebral plates without significantly reducing height. Both autosomal dominant and recessive forms of MED have been described.

Maroteaux distinguishes between Type I where the spine is normal or minimally affected but the epiphyses of the long bones, hands and feet are abnormal, Type II in which the hands and feet are normal, and Type III, the localised forms where several abnormal epiphyses may be localised to a particular region, e.g. Thiemann's disease affecting the epiphyses of the hands and feet.

In Group II are included dysplasias with generalised platyspondyly and accompanying shortness of the trunk. These are also further subdivided into several types, one of which includes Morquio's disease (mucopolysaccharidosis IV).

Group III, were termed by Maroteaux the epiphysometaphyseal dysplasias. They are characterised by minimal spinal lesions but abnormal epi physes with irregular metaphyses. This group Maroteaux[115] further subdivided into 2 classes, one of which is the pseudoachondroplastic type with

moderate vertebral abnormalities but lesions in the epiphyses and metaphyses producing extreme limb shortening. Maroteaux, however, states that despite the classifications of these disorders into three distinct groups, a spectrum of conditions exist with overlap between the three groups.

A more recent and very detailed classification of the epiphyseal dysplasias as that of Bailey[8], 1973. MED and SED are discussed as two distinct groups although Bailey, too recognises that overlap between these two conditions is commonly found Morquio's disease is included with the mucopolysaccharidoses although 4 types of Pseudo-Morquio's disease are included in the SED class.

In this classification the "congenita" and "tarda" forms of MED and SED are again considered separately. The disorders to be considered in the differential diagnosis of MJD, are, of course, the "tarda" group.

Within the MED Tarda category, Bailey[8] differentiates a number of types and subtypes. This differentiation is based on varying patterns of joint involvement and inheritance.

Bailey's classification of the MED and SED conditions may be seen in Table XXXXVII.

TABLE XXXXVII : CLASSIFICATION OF THE TARDA FORMS OF MED AND SED
(after Bailey, 1973)

MULTIPLE EPIPHYSEAL DYSPLASIA TARDA

Type 1 Lower limb, spine and upper limb involvement.

(a) Fairbank's MEDT: autosomal dominant.

(b) Pseudo-achondroplastic form - inheritance unknown

(c) Ribbings MEDT - autosomal recessive

(d) Maroteaux'MEDT - autosomal recessive and dominant.

(e) Juberg's MEDT - autosomal recessive.

Type II Lower limb and spinal involvement.

(a) Weinberg's MEDT.

Type III Lower limb and upper limb involvement.

(a) Thiemanns disease.

(b) Dietrich's disease

(c) Elbow - Knee MEDT

(d) Elsbach's dysplasia

Type IV Lower limb involvement

(a) Orkels MEDT.

Types V, VI, VII are other theoretical types of which Bailey has not seen cases.

Type VIII represent a miscellaneous category for cases which cannot be pigeonholed into any of the above categories.

SPONDYLO-EPIPHYSEAL DYSPLASIA (excluding the congenita forms).

The pseudo-achondroplasias

Types I to IV have been differentiated

The pseudo-Morquio's. Again four types have been recorded.

The SED tarda syndromes.

(a) X-linked SEDT.

(b) Brachyolmia.

(c) Brachyraphia

In the absence of any identified biochemical derangement, classifications will of necessity be based on anatomical descriptions and modes of inheritance and it is possible that types now considered to be separate will be found to be due to a common metabolic disorder.

Electronmicroscopy of epiphyseal cartilage has led to identification of a specific ultra structural storage defect in patients with pseudoachondroplastic dwarfism[37, 107]. This adds support to Bailey's[8] comment that as diagnostic methods improve most cases of MED may be shown to belong to Type I, and the distinction between MEDT and SED will become less obvious.

In this context reported pedigrees such as that of Diamond[43] are significant. It is for this reason that an attempt to further categorise MJD into a type or subtype of the epiphyseal dysplasias would appear to be of no real value.

MANAGEMENT OF THE PATIENT WITH EPIPHYSEAL DYSPLASIA

Although several authors[61,81] have stated that disability in multiple epiphyseal dysplasia is minimal, many others[130, 151, 147] have pointed out the tendency to the development of disabling precocious osteoarthrosis.

Physiotherapy in the early stages has been found to be of benefit both symptomatically and in reducing subsequent disability[12, 172]. Ribbing[147] emphasised that substitution of highter work for hard physical labour resulted in lesser degree of disability in later life. Jacobs[83] stated that osteotomy to correct deformities such as genu valgum would possibly

slow the development of degenerative changes. Weinberg[175] emphasised that osteotomy should be delayed till the mid-teens toward the end of the growth period as earlier surgery often necessitated repeat surgery later.

OTHER CAUSES OF EPIPHYSEAL DYSPLASIA

Isolated epiphyseal dysplasia of the proximal tibial epiphysis has been produced by Hurley and Asling[80] in the offspring of rats fed a manganese deficient diet. Zinc deficiency had been implicated in certain forms of dwarfism. It is apparent that a long-term study of trace elements will be of importance in relation to MJD even though no trace element deficiency at the present time has been found in the subjects studied.

SECTION V :

DISCUSSION AND

CONCLUSION

THE SOCIO-ECONOMIC IMPLICATION OF MSELENI JOINT DISEASE

Approximately 550 adults and children out of a total population of some 4,500 people are disabled to a lesser or greater extent by MJD. In a primitive community which lives almost entirely on the meagre crops produced by unsophisticated farming methods from a soil poor in nutrients and distant from water sources, this disablement becomes a problem of a major significance.

What can be done to alleviate the situation?
It is obvious that the problem must be approched from two directions. The first is the consideration of available methods to aid the individual affected by the disease. From an economic point of view, disability grants and pensions are paid to the more severely disabled patients and this aspect is not the primary concern of this thesis. From a medical point of view, an urban patient with bilateral osteoarthrosis of the hips as seen in the Mseleni people would be offered some form of surgical treatment, possibly Charnley arthroplasty. In this unsophisticated rural population where surgery is viewed with suspicion, for this reason and on obvious grounds of logistics, this is not a practical solution. At present there is no easy answer to this problem and the symptomatic treatment of pain is all that the majority of patients are offered.

The second and perhaps most important line of approach is to define the exact aetiology of MJD in order that the development of this disorder in the future generations may be prevented. This has been the objective of the Mseleni studies to date. The essence of the problem is whether the disease is environmental or hereditary?

MSELENI DISEASE : HEREDITARY OR ENVIRONMENTAL

MJD on both clinical and radiological grounds must be classified with the MED/SED group of conditions. However, the vital question remains unsolved. Is MJD a true hereditary disorder of bone or dysplasia or is it an environmentally induced phenocopy?

The situation of a musculoskeletal disorder occurring with a high prevalence in a specific geographical area is not unique to Mseleni. Kashin Beck disease represents a classical example of such a disorder where an environmental factor has been implicated. In South Africa a further example of a bone disorder of environmental origin may be seen in Kenhardt Bone Disease.

Originally described by Dodd et al.[44] in 1960, this disorder was found to occur in a localised community near Kenhardt in the north-east Cape. In a later report Jackson[82] concluded that the condition was related to the high chloride content of the community's drinking water modified by another undiscovered environmental factor.

Kuskokwim disease[142] is an example of a muculoskeletal disorder occurring in a specific population (Alaskan Eskimoes) which is almost certainly genetic in origin. This arthrogrypotic condition is one of several hereditary conditions found in isolated Eskimo populations.

Unusual gene frequencies of certain serogenetic markers[154] are an indication that random genetic drift has occurred within this population group.

In the case of MJD , some supportive evidence for a genetic hypothesis has been found. The disease is clearly familial. The disease pattern in genealogies investigated was compatible with an autosomal dominant inheritance of high penetrance. On clinical and radiological grounds the disorder closely resembles the MEDT/SEDT group of conditions.

However, there are unresolved problems. It is not clear how a disease could attain so great a prevalence in a population without evidence of founder effect. The absence of random genetic drift is thus a pointer against a genetic cause. Another strange feature is the apparent excess of affected females in the population when family studies have revealed no difference in the proportion of male and female offspring that are affected. This could however represent bias in sampling.

It is apparent therefore that no definite aetiology for MJD has been found. Despite the evidence in favour of a genetic aetiology, it would be unwise to conclude that the disease is indeed hereditary without an extremely extensive study of all aspects of the Mseleni environment. This is particularly true where peculiarities such as sex difference in prevalence remain to be explained. Pitfalls may await the unwary who invokes variation in penetrance and expressivity or unusual genetic mechanisms to support a genetic hypothesis. Kuru[62] which was thought to be a genetic disorder but now is believed to be due to a virus transmitted by cannibalistic practices[122] is a classical example.

It is the author's opinion that, given the limitations of working with an unsophisticated population in an area remote from a major hospital, investigating a disease with a variable age of onset, this problem

cannot be solved by a short term investigation over a fixed point in time. It is also apparent that vast resources of manpower and funds cannot be directed for an indefinite period of time to a single project.

The view of this author is that if a conclusive answer to the Mseleni problem is to be obtained, it will only be after an intensive in depth environmental study coupled with a long term follow-up of the present population for which minimal resources are required though over a extended period of time. A proposed concept for such future investigations is indicated diagrammatically in Fig. 57.

THE FUTURE OF THE MSELENI JOINT DISEASE PROJECT

MJD has been shown to be a condition phenotypically similar to the hereditary epiphyseal dysplasias. Although there is evidence to support the theory of an autosomal dominant hereditary form of transmission for this disorder, contradictory facts exist and a genetic aetiology has not been conclusively proven.

Since the possibility cannot be discounted that MJD may be an environmentally induced phenocopy of the hereditary disease, and would therefore be potentially preventable, an extensive search for such an environmental factor is mandatory. Although preliminary investigations into food and water supplies provided no real leads, it is obvious that a search for an environmental factor would require an extensive study of habits of the population. It is apparent that such a survey must be combined with a prospective long-term study of the population.

The concept proposed by the author for future study of MJD involves a two phase investigation. Four population groups would be studied in both phases. These would be an affected and a control group from the control area. The control group from both areas would be the inhabitants of a sample of "control kraals" in which no one has MJD. The affected group would be the inhabitants of a sample of "affected kraals" in which several people, preferably including at least one child, has MJD.

A Central Mseleni Study Project Registry, the responsibility of an epidemiologist would co-ordinate field-work and liaise with external organisations who would carry out necessary analyses:

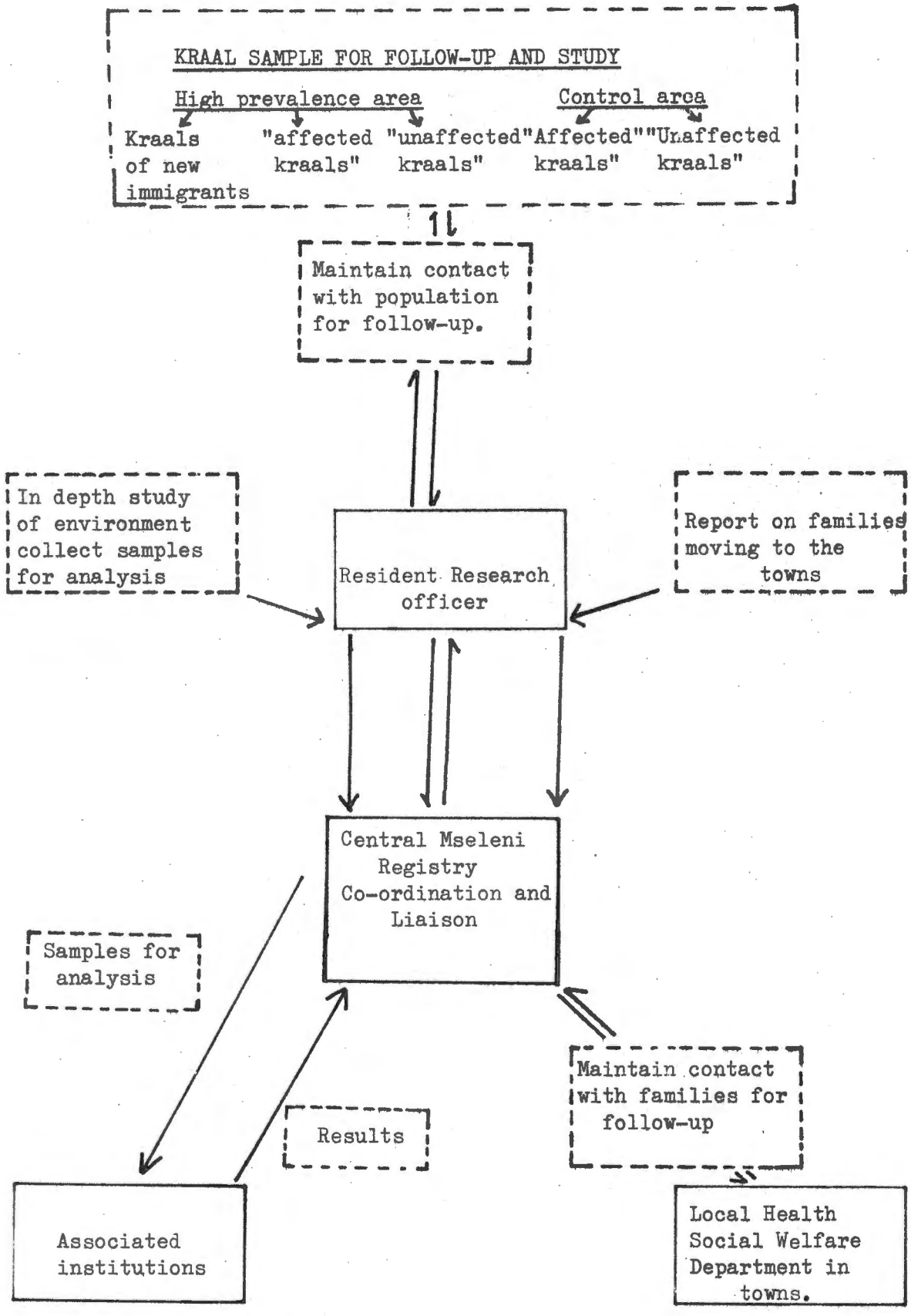

FIGURE 57 : Proposed concept for a long term follow-up project.

Phase 1 would be an intensive indepth study of the minutiae of the day-to-day living habits in the four subgroups of the population. During this phase which would last for a minimum of a year, to allow for any seasonal effects, a research officer would be permanently resident in the Mseleni area in order to gather demographic data and observe and compare customs, such as food storage and preparation, between the four groups of kraals.

Samples of substances ingested by the people would be collected for analysis and toxicological tests.

Phase 2 would be a long term study of selected families which would need little in the way of manpower or resources but necessitates long range planning and co-ordination over a minimum of ten years.

Families from the four groups of kraals would be observed for the development of joint disease in children and normal adults. Persons from outside the high prevalence area marrying into a kraal within the area should be noted and the development of joint disease in these persons or their offspring should be studied. Similarly affected people who move to the towns should be registered and followed up through liaison with the local health or social welfare department to observe whether their offspring develop MJD.

It may be argued that in a country where children are still dying of malnutrition a study such as this must be of low priority. However, resources thus needed, though required over a long period of time, would not be great.

Moreover, this disease causes great morbidity and disability to some 500 people.

The relationship of MJD to the hereditary epiphyseal dysplasias is not clear but it is established that the clinical and radiological picture closely resembles this group of conditions. Any aetiological factor or biochemical disturbance discovered in the Mseleni context may well have far-reaching implications in the field of bone growth and development.

C O N C L U S I O N

Mseleni Joint Disease is a disorder which clinically and radiologically may be classified with the Multiple Epiphyseal Dysplasia Tarsa and Spondylo Epiphyseal Dysplasia Tarda group of conditions. It is a familial disease which may be of genetic or environmental origin. No definite aetiological factor has been found.

It is my belief that no conclusive answer to the Mseleni problem will be found until a further intensive environmental study, coupled with a long-term follow-up of the present population has been completed.

PRETORIA

January, 1974.

/EDA

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APPENDIX

9058/48

HD BI

NATIONAL RESEARCH INSTITUTE FOR NUTRITIONAL DISEASES

of the South African Medical Research Council.

DIVISION OF MEDICAL STATISTICS AND EPIDEMIOLOGY

Family History Questionnaire

(Women's Questionnaire)

Name: .. .. Maiden Name: .. ..

Age: .. .. Sex: .. ..

Area: .. .. Section: .. ..

Kraal: .. .. Kraal head: .. ..

Married: .. .. Yes ☐ No ☐ Widowed ☐ Deserted ☐

Hip disease: .. .. Yes ☐ No ☐

Name of Husband: .. ..

Hip disease: .. .. Yes ☐ No ☐

Number of children: .. .. Boys: Alive ☐ Dead ☐

Girls: Alive ☐ Dead ☐

OTHER WIVES OF HUSBAND*

Name	Hip disease		Maiden name	Father's name	Children			
					Boys		Girls	
	Yes	No			Alive	Dead	Alive	Dead
1.	.. .. ..		.. ..	.. ..	.. .. ..		.. .. ..	
2.	.. .. ..		.. ..	.. ..	.. .. ..		.. .. ..	
3.	.. .. ..		.. ..	.. ..	.. .. ..		.. .. ..	
4.	.. .. ..		.. ..	.. ..	.. .. ..		.. .. ..	
5.	.. .. ..		.. ..	.. ..	.. .. ..		.. .. ..	
6.	.. .. ..		.. ..	.. ..	.. .. ..		.. .. ..	
7.	.. .. ..		.. ..	.. ..	.. .. ..		.. .. ..	
8.	.. .. ..		.. ..	.. ..	.. .. ..		.. .. ..	
9.	.. .. ..		.. ..	.. ..	.. .. ..		.. .. ..	

SUBJECT'S RELATION:

RELATION	NAME	Approx. AGE	HIP DISEASE			AREA OF ORIGIN	MAIDEN NAME	NO. OF BOYS		NO. OF GIRLS	
			Yes	No	Dwarfs			Alive	Dead	Alive	Dead
OTHER											
ATHER							xxxxxxxxxxxxxxxxxxxxxxxx				
OTHER'S MOTHER											
OTHER'S FATHER							xxxxxxxxxxxxxxxxxxxxxxxx				
ATHER'S MOTHER											
ATHER'S FATHER							xxxxxxxxxxxxxxxxxxxxxxxx				

FORM 2 IS USED IN HD A for relations of the male subject.

HD B for relations of the female subject and later (after page 14)

HD C for relations of the subject i.e. a wife.

CHILDREN OF FEMALE SUBJECT OR WIFE

WIFE'S NAME/ SUBJECT'S NAME.	Birth order	CHILDREN'S NAMES	SEX	HIP DISEASE			Approx AGE	ALIVE		MARRIED		HUSBAND/WIFE'S NAME	AREA	KRAAL HEAD
				Yes	No	Dwarfs		Yes	No	Yes	No			

TRUE SISTERS:

NAME	MAIDEN NAME	HIP DISEASE			HUSBAND'S NAME	Kraal	Section	Area	HIP DISEASE			CHILDREN'S NAMES	SEX	HIP DISEASE		
		Yes	No	Dwarfs					Yes	No	Un-sure			Yes	No	Dwarfs

TRUE BROTHERS:

NAME	KRAAL	SECTION	AREA	HIP DISEASE			WIFE'S NAMES	MAIDEN NAMES	HIP DISEASE			CHILDREN'S NAMES	SEX	HIP DISEASE		
				Yes	No	Dwarfs			Yes	No	Un-sure			Yes	No	Dwarfs

STEP BROTHERS:

NAME	HIP DISEASE			PRESENT AREA	SECTION	KRAAL	MOTHER'S NAME	HIP DISEASE			WIFE'S NAMES
	Yes	No	Un-sure					Yes	No	Un-sure	

STEP SISTERS:

RESENT NAME	HIP DISEASE			MAIDEN NAME	MOTHER'S NAME	HIP DISEASE			HUSBAND'S NAME	AREA	No. of Boys		No. of Girls	
	Yes	No	Un-sure			Yes	No	Un-sure			ALIVE	DEAD	ALIVE	DEAD

TRUE SISTERS OF FATHER

Name	Maiden Name	Hip Disease			Husband's name	Kraal	Section	Area	Hip Disease			Children's names	Sex	Hip Disease		
		Yes	No	Dwarf					Yes	No	Dwarf			Yes	No	Dwarf

TRUE BROTHERS OF FATHER

Name	Kraal	Section	Area	Hip Disease			Wife's names	Maiden Names	Hip Disease			Children's names.	Sex	Hip Disease		
				Yes	No	Dwarf			Yes	No	Dwarf			Yes	No	Dwarf

FATHER'S STEP BROTHERS:

MOTHER'S NAME	NAME	AGE	HIP DISEASE			KRAAL	ALIVE		AREA	NO. OF WIVES		NO. OF BOYS		NO. OF GIRLS	
			Yes	No	Dwarfs		Yes	No		Alive	Dead	Alive	Dead	Alive	Dead

FATHER'S STEP SISTERS

OTHER'S NAME	NAME	AGE	HIP DISEASE			KRAAL	ALIVE		AREA	MAIDEN NAME	NO. OF BOYS		NO. OF GIRLS	
			Yes	No	Dwarfs		Yes	No			Alive	Dead	Alive	Dead

TRUE SISTERS OF MOTHER

Name	Maiden Name	Hip Disease			Husband's name	Kraal	Section	Area	Hip Disease			Children's names	Sex	Hip Disease		
		Yes	No	Dwarf					Yes	No	Dwarf			Yes	No	Dwarf

TRUE BROTHERS OF MOTHER

Name	Kraal	Section	Area	Hip Disease			Wife's names	Maiden name	Hip Disease			Children's names	Sex	Hip Disease		
				Yes	No	Dwarf			Yes	No	Dwarf			Yes	No	Dwarf

Stepbrother of mother

Name	Hip Disease			Present Area	Section	Kraal	Mother's Name	Hip Disease			Wife's names
	Yes	No	Dwarf					Yes	No	Dwarf	

STEPSISTERS OF MOTHER

Present names	Hip Disease			Maiden name	Mother's name	Hip Disease			Husband's name	Area	Hip Disease			No. of Girls	
	Yes	No	Dwarf			Yes	No	Dwarf			Yes	No	Dwarf	Alive	Dead

GRANDCHILDREN OF SUBJECT (i.e. children of the married children listed on page 3).

Child's Name	Age	Hip Disease	Spouse	Hip Disease	Children's Names	Age	Sex	Hip Disease	Area	Section	Kraal

NAME ..... No. enumeration form .....

AGE .... Sex ..... DEGREE OF DEFORMITY: .....

WHICH JOINTS ARE AFFECTED ? .....

ONSET OF JOINT DISEASE ..... (Years ago)

AGE AT ONSET ..... PRE-SCHOOL

..... SCHOOL GOING

..... POST SCHOOL WITHOUT CHILDREN

..... MIDDLE AGED

..... OLD MAN/WOMAN

FOR FEMALES:

DID JOINT DISEASE COMMENCE:

... AS A YOUNG CHILD

... AFTER MENSTRUATION BEGAN

... AFTER MARRIAGE BUT BEFORE FIRST BABY

... AFTER FIRST BABY AND BEFORE SECOND BABY

... AFTER TWO OR MORE BABIES WERE BORN

HAVE YOU BEEN X-RAYED FOR JOINT DISEASE? YES/NO

IN WHICH JOINTS WAS PAIN FELT? First .....
Second .....
Third .....

DID THE PAIN START DURING AN ACUTE ILLNESS? YES/NO

DID PAIN START GRADUALLY? YES/NO

IF ASSOCIATED WITH AN ACUTE ILLNESS, DESCRIBE .....

.....

.....

DID ANYBODY IN YOUR FAMILY START WITH PAIN AT THE SAME TIME AS YOU DID?

YES/NO. IF YES, WHO .....

.....

are there any dwarfs in your family: Yes:No.

RELATIONSHIP (e.g. Mother, Father, Sister) .....

.....

.....

DO YOU KNOW OF ANY ABNORMAL CHILDREN IN YOUR FAMILY: YES/NO.

DETAILS: .....

.....

.....

HOW DOES YOUR JOINT DISEASE AFFECT YOUR DAILY LIFE? .....

.....

DOES ANYBODY ELSE IN YOUR FAMILY BUT NOT LIVING IN YOUR KRAAL SUFFER FROM JOINT DISEASE?

No	NAME	AGE	SEX	RELATION	AREA

KEY FOR DEGREE OF DEFORMITY

1 = Pain only in joints

2 = Walks with difficulty (No stick)

3 = Can only walk with aid of stick

4 = Crawls on hands and knees

5 = Immobile