HEREDITARY MULTIPLE EXOSTOSIS.

A STUDY IN ABNORMAL BONE GROWTH.

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S U M M A R Y

of a Thesis entitled

H E R E D I T A R Y M U L T I P L E E X O S T O S I S

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PART I. INTRODUCTION AND HISTORICAL REVIEW.

INTRODUCTION

Hereditary multiple exostosis is a generalised, heritable disorder of bone, characterised by the appearance of numerous cartilage-capped exostoses at the juxta-epiphysial regions of the endochondral skeleton. The condition was apparently known even in Hunter's day and most of its characteristic features were described before the end of the nineteenth century.

Nevertheless, the evolution of these curious lesions, their unusual distribution and the associated abnormalities of growth are still incompletely defined and largely unexplained.

Jaffe (1958) has suggested that 25 per cent of these cases eventually develop a chondrosarcoma, a statement which (considering Jaffe's authority) requires careful consideration.

A study of the hereditary characteristics of the disease in 1,124 cases collected from the literature by Stocks and Barrington in 1925 was marred by inaccuracies in most of the earlier papers on which they drew. Yet in the absence of sufficient evidence to the contrary their conclusions have gradually become entrenched in the description of the disease. No other significant analysis of any large series has been undertaken since then and the subject requires re-evaluation.

These are the reasons which stimulated the present study, undertaken at the Royal National Orthopaedic Hospital and the Hospital for Sick Children, Great Ormond Street, London.

CHAPTER I. HISTORICAL REVIEW.

A detailed historical review of the subject is presented. Palaeopathological studies relating to bone lesions in general and exostoses in particular are discussed.

Descriptions of "exostosis" in early medical writings are referred to. The first reference to multiple exostosis as a disease of young people, "constitutionally interwoven with the formation of bones", occurs in Hunter's lectures of 1786 and the first full case description was published by Boyer in 1814. The works of Virchow (1863), Bessel-Hagen (1891), Keith (1920) and Jaffe (1943) mark the milestones in the further development of knowledge about the disease.

CHAPTER II. NOMENCLATURE.

The confused nomenclature is recalled and an acceptable terminology is presented.

CHAPTER III. MATERIAL AND METHODS

A full description is given of the material studied and the methods employed. Fifty-two index patients formed the nucleus of the investigation. For the Genetic Studies another 84 relatives of propositi were examined and the pedigrees of 39 families were traced over at least three generations.

Growth Studies included a full anthropometric examination of 76 subjects. The methods employed and the standards used are discussed.

Normal Bone Growth was studied in foetal and autopsy material by standard histological and microradiographic techniques. Autoradiograph of the epiphysial plates in rabbits was also carried out.

PART II. CLINICAL, RADIOLOGICAL, AND MORBID ANATOMICAL ASPECTS OF HEREDITARY MULTIPLE EXOSTOSIS

CHAPTER IV. INCIDENCE.

A. The Frequency of hereditary multiple exostosis;

B. The Age Distribution at first appearance; and

C. The Sex Distribution of the abnormality are examined.

Reports in the literature are compared with the present series of cases.

CHAPTER V. CLINICAL PRESENTATION.

A full description of the lesions in hereditary mutiple exostosis is given. These include the juxta-epiphysial exostoses and certain deformities resulting from the abnormality of growth. The most important of these are bowing of the radius, subluxation of the radio-humeral joint and valgus deformities of the knee and ankle.

CHAPTER VI. RADIOLOGICAL FEATURES.

The radiographic appearances of the lesions are described and illustrated by radiographs of the present series of patients.

CHAPTER VII. DIFFERENTIAL DIAGNOSIS.

The one condition persistently confused with hereditary multiple exostosis is dyschondroplasia. This is a distinct and separate entity and the distinguishing features are described in this chapter.

CHAPTER VIII. PATHOLOGY.

The morbid anatomy and the microscopic appearances of the cartilage-capped exostoses are described and illustrated. The nature of the lesions as abnormalities of growth, rather than true neoplasms, is emphasised. After growth has ceased most of the cartilage ossifies,

though islands of cartilage tissue may become trapped in the bony trabeculae of the exostosis, there to lie dormant and possibly to become active again in adult life.

CHAPTER IX. COMPLICATIONS.

The following complications were encountered:

Interference with function, which may be due to impingement of exostoses on adjacent bones, interference with tendons, or certain associated deformities.

Pressure effects on organs adjacent to large exostoses.

Fracture of the exostosis.

Exostosis Bursata.

Chondrosarcoma.

CHAPTER X. TREATMENT.

The indications for treatment are discussed and the post-operative complications in these patients are listed.

CHAPTER XI. CHONDROSARCOMA.

This most serious complication was described in the very earliest case history of multiple exostosis. It is believed, by Jaffe, to occur in as many as 25 per cent of such patients.

Twenty-three reliably documented cases in the literature are reviewed, together with five cases known to the author.

Incidence, age and sex distribution, the sites affected are all discussed. The clinical, radiological and morbid anatomical features are described and related to illustrative cases in this series.

PART III. "ANTECEDENTS AND CONSEQUENCES"

This section attempts to explain the nature of the disease, the genetic pattern in which it operates, the way in which it affects bone growth and is, itself, defined by the normal mechanisms of growth and ossification -- in the words of Teilhard de Chardin, "to establish a coherent order between antecedents and consequences".

CHAPTER XII. HEREDITARY CHARACTERISTICS.

The most significant and widely influential genetic study on hereditary multiple exostosis was that of Stocks and Barrington (1925). From a simple analysis of 1,124 cases reported in the literature they concluded that the disease was inherited in two-thirds of all cases; that a transmitting father was always affected himself but that females could transmit the disease without being affected; and that the sex ratio showed a 7:3 preponderance of males.

Harris (1948) suggested that these findings could be explained by the existence of a second, autosomal modifying gene which suppressed the disease in certain females. On testing this hypothesis against Stocks and Barrington's data good agreement was obtained.

It is the author's contention, however, that these conclusions are questionable in view of the inaccuracies of many of the reports from which the data was derived. A similar analysis of the 39 families in the present series was carried out. The findings here suggest that, in the majority of cases the disease is transmitted directly by an autosomal dominant gene which always produces detectable

effects in the heterozygote. There was complete manifestation in males and females alike with no instance of an unaffected mother transmitting the disease to her offspring. Males and females were affected with equal frequency.

CHAPTER XIII. NORMAL BONE GROWTH.

An appreciation of normal bone growth is believed to be essential for a full understanding of a developmental abnormality such as multiple exostosis and the arguments used in discussing its pathogenesis.

Endochondral ossification and growth of the tubular bones and the small, irregular bones of the carpus and tarsus were studied in the human foetus and in autopsy specimens. In particular the organization and growth of the epiphysial plate were examined. Autoradiographic studies in rabbits failed to elucidate the mechanism of transverse growth of the epiphysial plate. However, more recent work on this problem, using tritiated thymidine, has since been reported and is discussed here.

CHAPTER XIV. THE EVOLUTION OF THE LESIONS.

The development of the exostoses are traced from their earliest appearance to the full-blown state. Their close relationship to cartilage growth and ossification is demonstrated and the abnormal patterns of growth are described.

CHAPTER XV. THE DISTRIBUTION OF THE LESIONS.

The lesions in multiple exostosis are strictly limited to bones developed in cartilage. However, whereas the tubular bones are

frequently involved, exostoses are rare in the tarsal and carpal bones, the patellae, the vertebral bodies and the sternum. These peculiarities have not been satisfactorily explained.

Radiographic examination at successive ages in patients of this series has shown that this selective distribution may be less a peculiarity of the disease than a reflection of certain differences in the normal process of growth at the different sites. It is suggested here that all bones developed in cartilage are equally exposed to the genetic disorder. The development of detectable lesions, however, is determined by the degree of elongation and modelling which the bone undergoes during growth.

CHAPTER XVI. BONE GROWTH IN DIAPHYSIAL ACLASIS.

The basic abnormality in diaphysial aclasis (multiple exostosis is a disorder of bone growth and this is reflected in the widespread abnormalities of the endochondral skeleton.

The results of a detailed anthropometric study of 76 patients with diaphysial aclasis are presented in this chapter under the following headings:

(1) Abnormal bone growth: (a) retardation of growth and
(b) adaptations of growth due to pressure by exostoses.

(2) Migrating exostoses.

(3) Disappearing exostoses.

It is shown here that most of the deformities of the tubular bones are due to the same underlying factor -- diminished length of the bones affected by the disease.

Migrating exostoses and disappearing exostoses are examples of the normal process of modelling applied in special circumstances.

CHAPTER XVII. THE PATHOGENESIS OF THE LESIONS.

Certain experiments aimed at inducing abnormal bone growth are discussed here. These include abnormalities following trauma to the epiphysial plate and exostoses following irradiation. The latter bear a strong resemblance to the lesions of diaphysial aclasis. Multiple exostoses have also been produced in experimental lathyrism in rats but these lesions are not related to the epiphysial discs.

The increased excretion of acid mucopolysaccharides in this disease has suggested a metabolic abnormality. This investigation was repeated and the results are discussed.

The work ends with a brief consideration of the more likely theoretical explanations of the basic growth defect, viewed in the light of the findings of this study.

TO JOAN,

who waited.

A C K N O W L E D G E M E N T S

It is an honour to express my gratitude to my teachers and mentors at the Royal National Orthopaedic Hospital, London, who provided the stimulus, the encouragement and the environment which made this work not only possible, but exciting. In particular I should like to thank Mr. H.J. Seddon, Director of Studies in the Institute of Orthopaedics; Mr. H. Jackson Burrows, Dean of the Institute of Orthopaedics; and Dr. H.A. Sissons of the Department of Morbid Anatomy.

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microradiography and assisted in the preparation of the microradiographs used to study normal bone development; Dr. C. Lack of the Institute of Orthopaedics, Stanmore, in whose department I was privileged to learn more about radio-isotopes and their uses in studying cartilage; and Mr. S.J. Ali of the same department for his advice on the estimation of urinary acid mucopolysaccharides.

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Most of the original photographs were prepared by Mr. R.J. Whitley of the Photographic Department of the Institute of Orthopaedics, London. The reproductions were made by Mr. A. Veenstra, Dept. of Surgery, University of the Witwatersrand. Mr. A.M. Shevitz, Dept. of Medicine (University of the Witwatersrand) photographed the pedigree charts. Mr. Ulrich, S.A. Institute for Medical Research, prepared the photomicrographs in Figure 23. Figures 5, 34 and 69 were drawn by my wife. The manuscript was typed by Miss R. Gittelson.

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CONTENTS

ILLUSTRATIONS

Figures

Figures Page.

TABLES

PART I

INTRODUCTION AND HISTORICAL REVIEW

INTRODUCTION

Hereditary multiple exostosis is a generalised, heritable disorder of bone, characterised by the appearance of numerous cartilage-capped exostoses at the juxta-epiphysial regions of the endochondral skeleton. This much is undisputed. The nature of the disease, the evolution of the exostoses, the peculiarities of their distribution, their relationship to neoplasia and malignant change, the associated skeletal deformities - even the straightforward details of the hereditary pattern are still subject to considerable disagreement and all, as yet are incompletely understood and largely unexplained.

The condition of "exostosis" has been known since, at least, the time of Hunter; the effects on bone growth and some of the visible deformities associated with the exostoses were described before the end of the nineteenth century. Yet, until the present study was commenced, no detailed, reliable anthropometric data from any significant series of these cases had been published. The basic defect - an abnormality of bone growth - has, with certain notable exceptions, received scant attention while the exostoses have commanded the field of vision.

These cartilage-capped exostoses, perceived in almost every dimension since the development of radiography, have almost invariably been defined in static terms. Excepting the outstanding works by Jaffe (76;77)and

Lichtenstein, (100) the evolution of these lesions over the full period of bone growth has seldom been described and nowhere has their unusual distribution been rationally explained.

Though not primarily neoplastic, the cartilaginous exostoses have long been known to give rise to chondrosarcoma in a significant proportion of cases. Jaffe, (77), one of the leading authorities on bone tumours, believes the incidence of this complication to be of the order of 25 per cent! That one out of every four of these patients will develop a chondrosarcoma seems incredible to most clinicians and this fact requires careful verification.

If the theories of the pathogenesis of hereditary multiple exostosis are, perforce, speculative, its genetic characteristics are open to objective study and analysis. One such investigation was undertaken by Stocks and Barrington in 1925 (135) in an exhaustive review of 1124 published cases. Unfortunately many of the earlier papers upon which they drew contain serious inaccuracies, particularly those from the period prior to the development of radiography. A re-analysis of their data by Harris in 1948 (69) did nothing to overcome this fundamental difficulty. The only other significant work on this subject, using modern statistical methods, was a genetic study of six families by Krooth, Macklin and Hilbish in 1961. (87). The entire subject requires a critical

re-evaluation.

These are the reasons which stimulated the investigation on which this thesis is based. The clinical, radiological, pathological, anthropometric and genetic studies of hereditary multiple exostosis were carried out between May, 1959 and July, 1962 at the Royal National Orthopaedic Hospital and the Great Ormond Street Hospital for Sick Children, London.

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The thesis is divided into three parts. The first is an introduction to and a historical review of the subject - the line of perspective that brings us to that point in time and the development of medical thought from which the condition is observed.

Part two essays a description of the disease, its clinical manifestations, radiological appearance and morbid anatomy - not merely as a prospect of probabilities, but rather as a detail of the composite picture derived from the study of many individuals.

The third part strives to explain the nature of the disease, the genetic pattern in which it operates, the way in which it affects bone growth and is, itself, defined by the normal mechanisms of growth and ossification - in the words of Teilhard de Chardin, "to establish a coherent order between antecedents and consequences."

C H A P T E R I.

HISTORICAL REVIEW.

"There is no great harm in the air of patronage with which our times in their self-satisfied enlightenment, address the great who were of old; but we do use droll adjectives! If these great ancients show the simplicity of perfect art, we call them naif ..... if they tickle our fancy, they are quaint; if we find them altogether satisfactory, both in form and substance, we adorn them with the epithet modern, which we somehow think is a superlative of eminence."

George Lyman Kittredge.

PALAEOPATHOLOGY.

The origin of disease is coincidental with the origin of life itself and dates back millions of years before the advent of man. Of all tissues the bones, preserved and fossilized in rock, provide the surest evidence of disease in prehistoric vertebrates. Among these ancient specimens, dating back to the Mesozoic Era and earlier, are numerous examples of exostosis. (37; 104 ; 105). Some of these were undoubtedly due to fracture and subsequent healing of the bone, giving the impression of multiple exostoses in different parts of

FIG. 1

Prehistoric scapula, with exostoses due to fracture. Reproduced from Moodie's Paleopathology (1923); Plate XXIII.

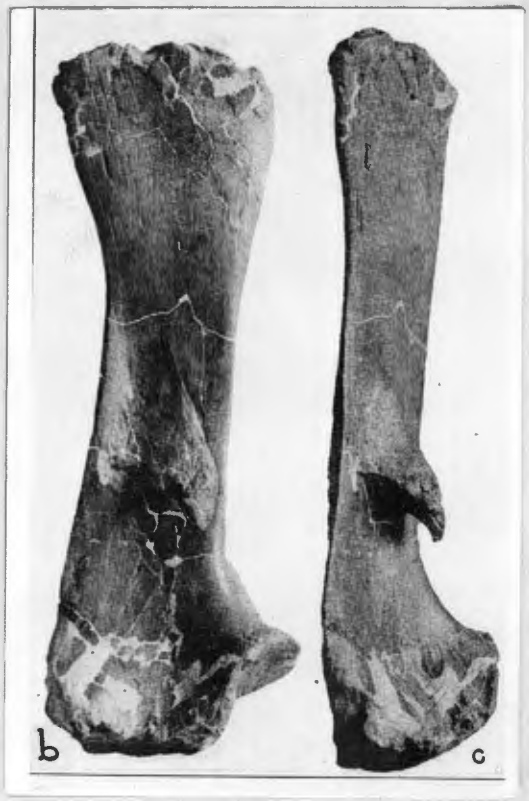


FIG. 2

Scapula of the dinosaur Triceratops. Reproduced from Moodie's Paleopathology (1923); Plate L.

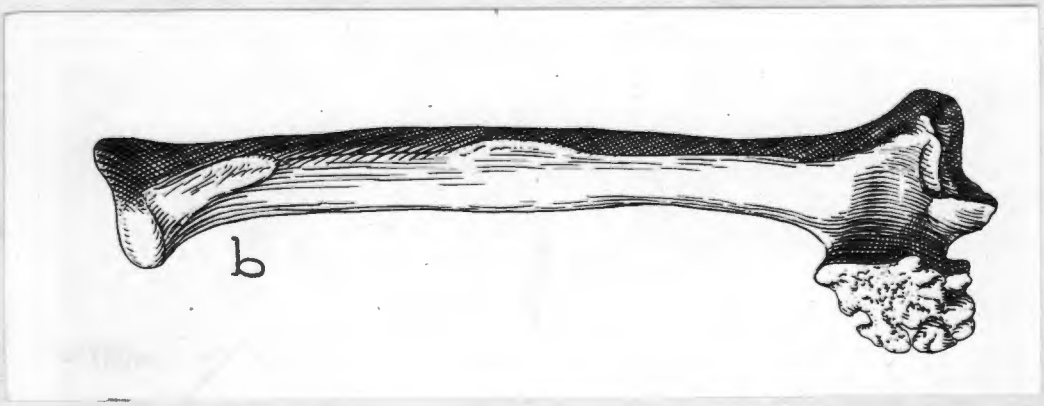


FIG. 3

Radius of Daphaenus felinus. At the distal end is a lobulated exostosis. Reproduced from Moodie's Paleopathology (1923); Plate LIII.

the skeleton (Fig. 1). Some, again, were due to osteo-arthritis and spondylitis, others are more difficult to explain and have been called, simply, "tumour" or "osteoma". The caudal vertebrae of the giant dinosaur (Apatosaurus) discovered in the Como beds, Comanchean, Wyoming, show a tumour at the intervertebral junction, thought to be neoplastic in origin (104) (though possibly the result of trauma or infection). An interesting lesion, not unlike the solitary exostosis seen in humans, is a horn-like exostosis on the scapula of the dinosaur Triceratops in the U.S. National Museum (Fig. 2). Even more remarkable are the radii of Daphaenus felinus, a species of dog dating from the Oligocene Period (2½ million years old) at the distal ends, bilaterally, are large, lobulated exostoses closely resembling the cartilage capped exostoses to be described later (Fig. 3).

Prehistoric Man.

The oldest known example of human pathology is an exostosis of the femur belonging to man's most ancient forbear. In 1891 Eugene Dubois, excavating among the volcanic deposits of Java, discovered a skull-cap, a femur and two teeth belonging to a primate "intermediate between the Anthropoids and Man" - Pithecanthropus Erectus. (36). The femur was complete; it measured 18 inches in length and at its proximal end was a large, pathological exostosis (Fig. 4).

FIG. 4

FIG. 4

Femur of Pithecanthropus Erectus, discovered by Dubois in 1891. Projecting from the medial aspect of the proximal end is a large exostosis, similar to that seen in modern man. (Figure after E. Dubois, 1894).

This specimen was discussed at a meeting of the Berlin Society of Anthropology and Ethnology (1895), where Virchow pointed out its close resemblance to the well known exostoses of modern man, and compared it with similar examples from the Berlin Pathological Institute (148).

Recent Man. The Ancient Egyptians.

The palaeopathology of the Ancient Egyptians, the races of Central Europe, the North American Indians and the Ancient Peruvians has been studied in considerable detail (105; 123; 124; 131)In addition to the human remains, there is the evidence of statues and statuettes, paintings and reliefs in tombs, illustrations on various ornaments and the recorded words of ancient scribes. Osseous lesions abound among this material and include bone tumours and exostoses of uncertain etiology (105; 126).

The most extensive of these studies was the palaeopathological survey of Nubia, carried out by G. Elliot Smith, F. Wood Jones and others in 1907-8 (131). Some 6,000 mummies were examined, covering all the periods from the Predynastic (10,000 - 3,400 B.C.) to the Roman. Fractures, bone infection, ankylosing spondylitis, rheumatoid arthritis and osteoarthritis appeared to be common in ancient Egypt; Smith and Ruffer have described a case of tuberculous spondylitis in a mummy of the 21st Dynasty (1100 B.C.). (126). An "osteogenic sarcoma" of

the distal femur was discovered in a mummy of the 5th Dynasty (2500 B.C.). (130). There is no convincing case of multiple exostosis in these records.

Sir Marc Armand Ruffer, the most dedicated of the palaeopathologists working in Egypt, gathered a wealth of information on osseous lesions in Ancient Egyptians (126). Among the skeletons discovered in the catacombs of Kom el Shougafa, Alexandria, dating from the early Christian period, he encountered a large tumour of the ischium thought to be an osteosarcoma, (124) but possibly a chondro-osseous tumour of which the cartilaginous parts had been destroyed. Another large pelvic exostosis was found among the Coptic bodies dating from the fifth and sixth centuries A.D. (123).

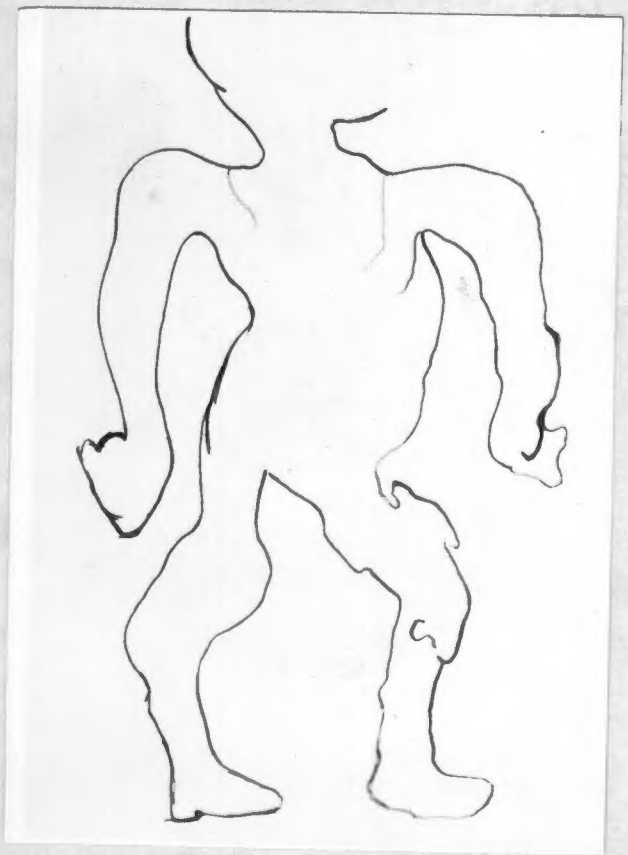


FIG. 5

Bas relief of the 1st Dynasty. After Ruffer (Studies in the Palaeopathology of Egypt; Plate IX, Fig. 16).

One of the most fascinating studies by the same worker concerns the dwarfs and other deformed persons depicted in the drawings and statuettes of the Egyptian tombs. (126). Among these, achondroplasia is the most easily recognisable. One figure in particular draws One's attention and is reproduced here (Fig. 5).

This is a bas-relief of the 1st Dynasty showing a dwarfed person with deformities of the arms and legs. Ruffer stated : "An exact diagnosis is in my opinion impossible. Considering the absence of any marked disproportion between the size of the body and that of the legs, considering also the well marked deformity of the legs, I conclude that the disease which has produced these deformities was probably rickets." (126).

Now, the studies of Elliot Smith and Wood Jones already referred to failed to reveal a single case of rickets among 6,000 bodies examined and led these workers (and others) (55; 63; 105) to conclude that rickets was unknown in Ancient Egypt.

It is submitted here that the figure which puzzled Ruffer could have been a case of multiple exostosis. This would have accounted for the shortening of the arms in the absence of any marked disproportion between the body and the lower limbs,as well as the lumpy appearance and deformities of the lower limbs. Moreover, the hands in this figure appear to be markedly deviated to the ulnar side, one of the most characteristic deformities of multiple exostosis (see later).

HIPPOCRATES TO THE PRESENT TIME.

Multiple exostosis, if it was known to the early physicians, was not described until the 18th Century. The works of Galen (131-200 A.D.) (52) and Paré (1510-1590) (115) bear only isolated references to exostotic lesions of bone. Severino (1580-1656) (127) , one of the earliest pathologists, illustrated a remarkable case of multiple chondromatosis (Fig. 6), a condition which has often been confused with multiple exostosis.

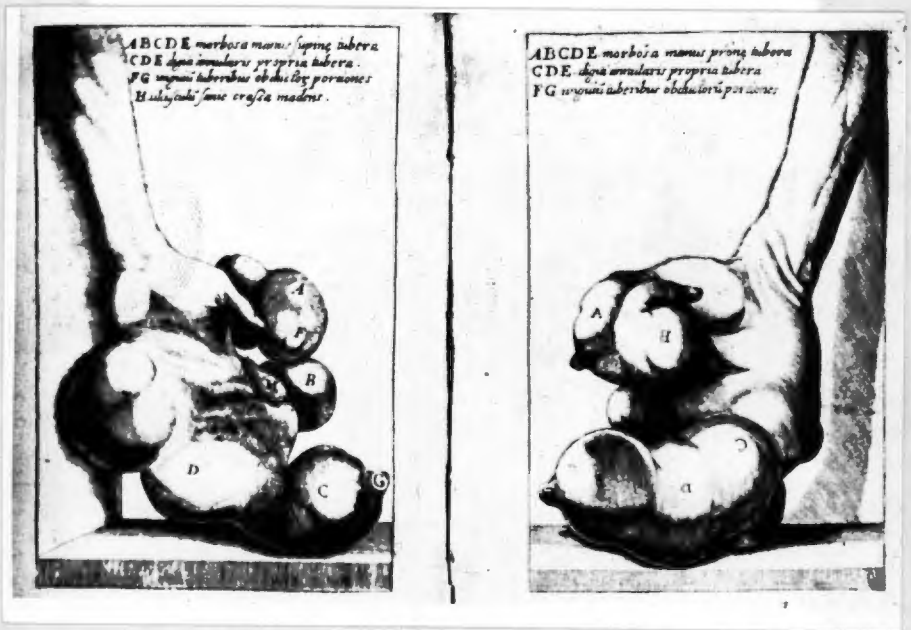
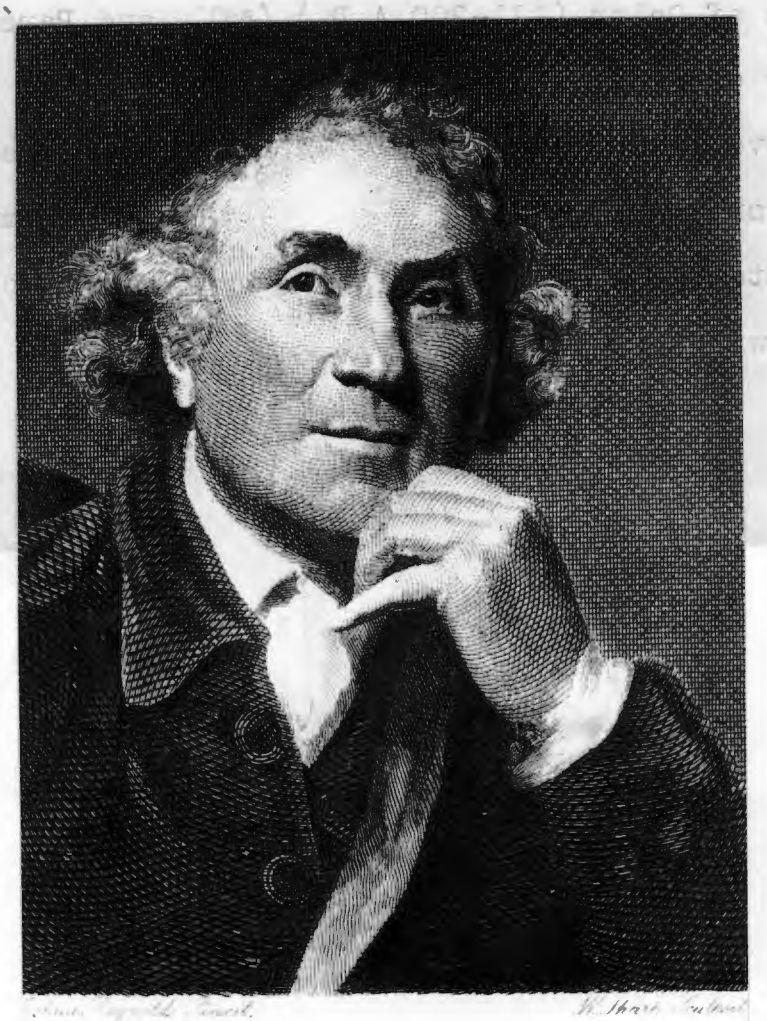


FIG. 6

An illustration reproduced from Severino's De Recondita Ascessum Natura (1632). The appearances are those of multiple enchondromata of the metacarpals and phalanges.



John Hunter

"That Excellent Practical Physician", Thomas Sydenham (1624-1689) warned of the consequences, including exostosis, that might follow syphilis (136).
Indeed, until after Hunter's time, "exostosis" was used merely as a descriptive term in a variety of conditions such as fractures, myositis ossificans, osteomyelitis, "caries of the bone", syphilis (venereal exostosis), osteoarthritis and certain unspecified bone tumours.((96; 119; 141). Benjamin Bell, the surgeon (1749-1806), divided exostoses into those produced "by a superabundant callus in fractured bones; by bones being deeply wounded, or their substance eroded by an ulcer", and those which appeared as "the symptom of some general affection of the system, particularly of the lues venerea and scrophula." (9).

The description of multiple exostosis as a distinct clinical and pathological entity begins with John Hunter (73). Far ahead of his contemporaries in this, as in most things, his understanding went straight to the heart of the matter. In the series of Lectures on the Principles of Surgery which he delivered in 1786 and 1787 he described exostosis as a disease "in a great measure peculiar to youth", and distinguished between those that affect one bone and those that affect "almost every bone in the body". He emphasized that it was not the result of inflammation, but appeared to be "constitutionally interwoven with the

formation of bones in such people." Their predilection for the bony extremities, and the associated enlargement of the bone ends led him to suppose that the condition was related to rickets.

Not surprisingly a similar understanding of the subject is reflected in the works of Hunter's pupils, Astley Cooper (26) and Abernethy (1). By this time, however, the first case histories had appeared in the medical literature.

In 1814 Boyer (17) published the first detailed description of a patient with hereditary multiple exostosis. This patient was a thirty-year old woman who had developed a chondrosarcoma in an exostosis at the distal end of the right femur, a circumstance which necessitated the amputation of her lower limb and provided Boyer with the opportunity of studying the morbid anatomy of this tumour and several smaller exostoses of the tibia and fibula. These he referred to as being "bony at the base, and cartilaginous elsewhere." The patient's children, her father, her brothers and sisters and nephews all had numerous "bony tubercles" on the ribs and the ends of the long bones.

A few years later (the case is not exactly dated) in the 'Lecons Orales' delivered at the Hôtel-Dieu, Dupuytren (38) described the case of a gardener, aged 18, who was found to have multiple exostoses "whilst still at the breast." The description leaves no doubt that this was a typical case of multiple exostosis.

Another detailed case history appeared in the Guy's Hospital Reports of the Lancet of July 23, 1825 (64) ushering in a long period during which isolated cases or families were presented before the medical societies of Europe.

A patient which Stanley showed at St. Bartholomew's Hospital in 1853 (134) was "an odd-looking, very short man, standing only about four feet eight in height, of fair complexion, and somewhat knock-kneed." Here is one of the earliest references to the deformities associated with the disease. For the most part, however, attention was centred on the cartilage-capped exostoses, the palpable evidence of disease which could be subjected to exact tabulation and measurement. Paget (1851 and 1870) (113; 114), Weber (1856 and 1866) (149; 150), Le Gros Clark (1863) (97), Von Recklinghausen (1866) (142), Cohnheim (1867) (23), Virchow (1863/4, 1876, 1891(145; 146; 147) all turned their attention for some while on these curious lesions.

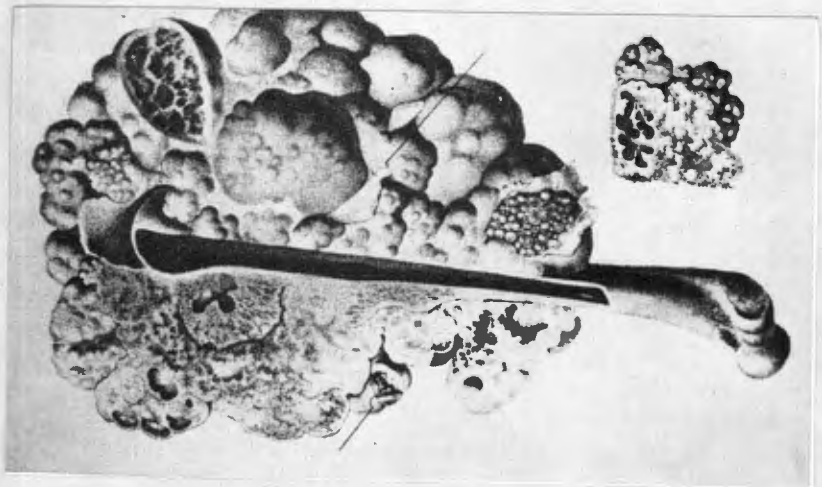


FIG. 7

Osteochondroma illustrated in Cruveilhier's atlas, Anatomie pathologique du corps humain (1830-1842).

The development of the improved microscope had by now unlocked the door to cellular pathology, with Virchow as the leading exponent of the new discipline (144). The gross pathology of cartilaginous tumours was well known (Fig. 7); their microscopic structure had recently been described by Johannes Müller (145). According to Virchow's theory all disease stemmed from cellular disorder, and pathology was "always based on histology." (144). It followed naturally that all cartilaginous tumours fell under the heading of Chondroma, which he subdivided into Enchondroma - those arising centrally within the spongiosa - and Ecchondrosis or Exostosis cartilaginae (those growing outwards from the cortex). (145; 146; 147). This idea formed the basis of one of Virchow's classic addresses (146) and later gave rise to the erroneous concept of multiple enchondromatosis and multiple exostosis as different and interchangeable manifestations of the same disease. With few exceptions this ambiguity pervaded the writings on the subject until very recent times.

In 1891 Bessel-Hagen (12) published a paper which still stands as one of the most detailed and perceptive accounts of hereditary multiple exostosis. He described the characteristic distribution of the lesions and all the important deformities of the disease, the relationship to chondrosarcoma and the importance of heredity in its etiology.

His clinical insight was the more remarkable considering that Roentgen only discovered "X-rays" four years later.

One of the earliest radiographic reproductions showing a characteristic lesion in a case of multiple exostosis appeared in the atlas of medical illustrations compiled by the New Sydenham Society in 1904 (6) (Fig. 8.) Described as "congenital absence of carpal end of the ulna," this is clearly one of the typical deformities of hereditary multiple exostosis.

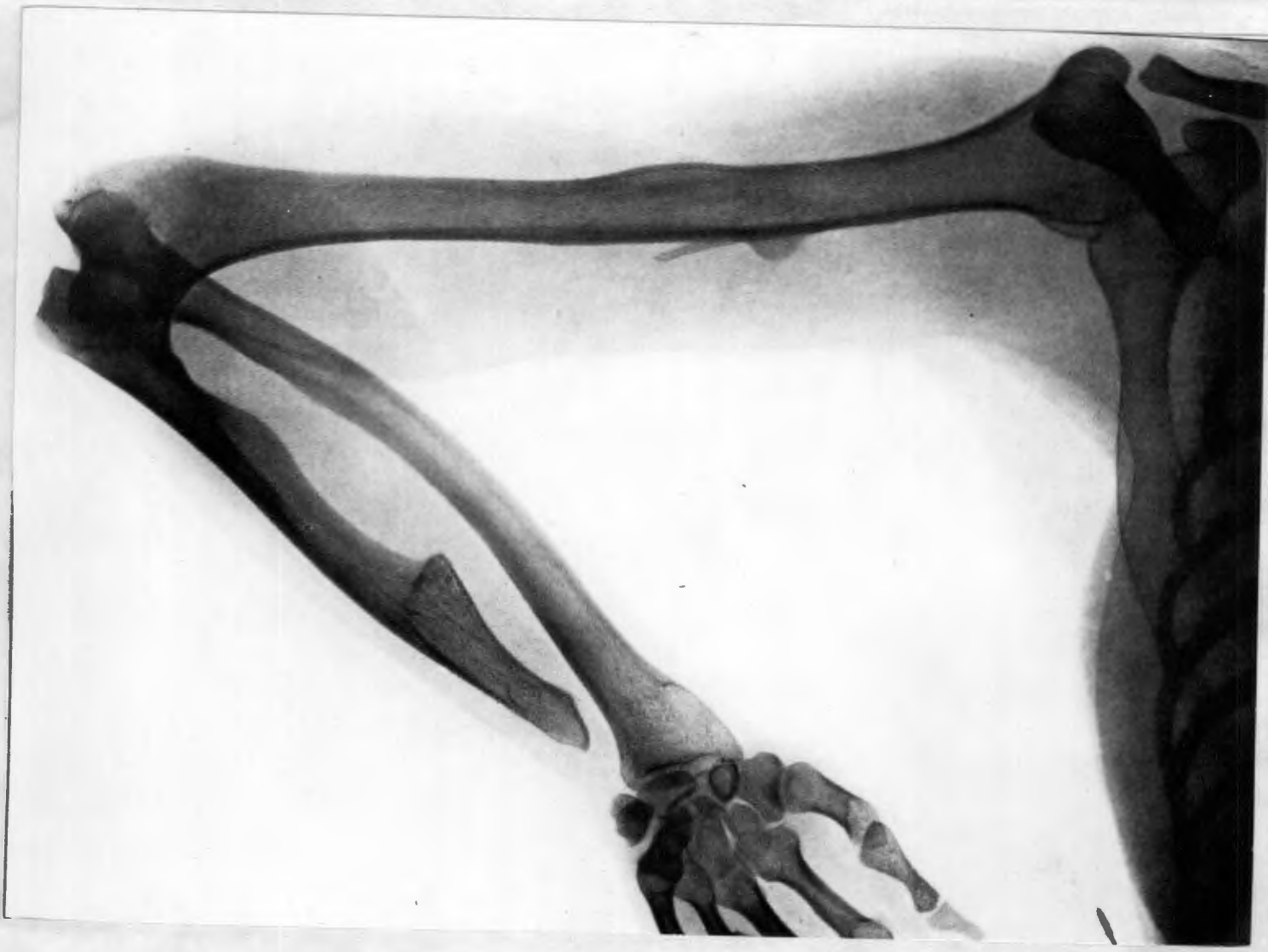


FIG. 8

Early radiograph showing "congenital absence of carpal end of the ulna".

Of its several manifestations, it was the widespread effect on bone growth that impressed Keith (1920) (83) when he first encountered the condition and led him to adopt the name "diaphysial aclasis", suggested to him by the writer, Morley Roberts, and still commonly used in Britain. He urged that the condition of multiple exostosis be removed altogether from the category of "tumours" and placed among the "disorders of growth."

In 1925, Stocks and Barrington (135) published their analysis of 1124 cases of multiple exostosis collected from the literature of the late 19th and early 20th centuries. Primarily a study in eugenics, this work is analysed in some detail in the section on Heredity. It served to lessen the obscurity surrounding the disease; the ambiguities remained, however, and have only gradually been untangled in recent years, most notably by Jaffe (1943; 1958). (76; 77).

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CHAPTER II.

NOMENCLATURE.

In 1915 Ehrenfried (40) drew attention to "a disease little known in this country (America)", though it had been introduced to the American literature by Gibney in 1875 (57). It went, as Ehrenfried put it, "under the obscure name of multiple cartilaginous exostoses." He was able to list 17 other names currently used to describe the disease, viz.: hereditary multiple exostoses, multiple cancellous exostoses, ossified diathesis, rachitiform enchondrosis, exostoses epiphysaires nombreuses, exostoses ostéogéniques multiples or héréditaires or familiales, exostoses juxta-epiphysaires or de croissance multiples, exostoses congénitales symmétriques nombreuses, dyschondroplasia, Ollier's disease, exostosis multiplex cartilaginea, chondral or exostotic dysplasia and multiple congenital osteochondromata. Since none of these terms commended itself to Ehrenfried he suggested a nineteenth - Hereditary Deforming Chondrodysplasia - which was generally adopted in the United States.

Five years later Keith (83), in England, called it Diaphysial Aclasis which, excepting a period during which it was commonly referred to as Keith's Aclasis, is the term most widely used in Britain.

Other terms occasionally used were multiple osteomata, multiple ecchondromata and chondrodystrophia foetalis.

An amusing note was struck by a case listed in the American Bone Sarcoma Registry as : "Hong Mun, colloquially known as Knobby Willy, the Exostotic Kid." (Case No. 668, 1925).

Much of this confusion arose because of the supposed relationship between multiple exostosis and multiple enchondromatosis (dyschondroplasia). Indeed, the radiographs illustrating Ehrenfried's paper (40) are clearly those of dyschondroplasia and not hereditary multiple exostosis. It is now known that these two conditions are quite distinct (46; 77) and the terms describing dyschondroplasia should not be applied to hereditary multiple exostosis.

Jaffe (1943) urged the use of the simple, descriptive term Hereditary Multiple Exostosis; this name and Diaphysial Aclasis are used interchangeably throughout the present thesis.

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CHAPTER III.

MATERIAL AND METHODS.

All available records at the Hospital for Sick Children and the Royal National Orthopaedic Hospital were collected for study if indexed under any of the following headings : hereditary multiple exostosis, multiple exostosis, diaphysial aclasis, exostosis, osteochondroma, ecchondroma, enchondroma, chondroma, chondromatosis, dyschondroplasia, Ollier's Disease, chondrosarcoma. In most instances an examination of the case notes and the available radiographs was sufficient to separate those with true multiple exostosis (diaphysial aclasis) from the others. Doubtful cases were not included until they had been examined by the author.

Records of 78 patients were found. Thirteen of these patients could not be traced at all; a further nine declined to attend for examination but completed questionnaires.

The remaining 56 patients formed the nucleus of this study; they are referred to as "index patients." Four of them have died, one as a result of this disease; the other 52 were examined in detail, clinically and radiologically. In each instance earlier radiographs were available for comparison and often the lesions could be traced from their earliest appearance to the present time.

GENETIC STUDIES.

Of the 52 index patients examined in detail, four were unable to give a reliable family history and two were adopted children. The remaining 46 patients belonged to 39 families in whom detailed pedigrees were charted over at least three generations (Appendix I). In each case the index patient (propositus) was interviewed and a tentative family-tree drawn up. Every report of an affected family member was followed up and confirmed, wherever possible, by either visiting the subject, writing to his doctor or obtaining a copy of his record from a hospital he had attended. Relatives said not to be affected by the condition were often not examined; complete verification of every negative report would have meant an unjustifiable intrusion on the individual's privacy. The exceptions to this rule were the reputedly unaffected parents of any children thought to have the disease. Since it is generally believed that unaffected females can pass the disease to their children, every effort was made to submit cases of this sort to radiological proof. Before completing the pedigree at least one member from an older or younger generation was interviewed and the information cross-checked against the original record.

Altogether 84 relatives of propositi were examined, 40 of them both clinically and radiologically and 44 clinically but not radiologically. These subjects are referred to as "secondary cases."

The pedigrees of these 39 families are illustrated in Appendix I.

GROWTH STUDIES.

Seventy-six subjects were examined in sufficient detail to be included in a study on bone growth and development in diaphysial aclasis. Their examination included a full radiographic survey of the skeleton and detailed measurements of height, weight, span, symphysial height and measurement of individual long bones. The skeletal age of every patient under 18 was estimated against the standards of Greulich and Pyle (1959)(61). When previous radiographs of the hand and wrist were available the skeletal age was estimated from these also, and correlated with the chronological age at that time. There are other methods of estimating skeletal maturity - all based on the characteristic appearances of the epiphysial ossification centres at different ages - but the method of Greulich and Pyle offers considerable advantages in a study of a generalised bone disease such as diaphysial aclasis. The reference standards consist of a large series of radiographs of the hand and wrist taken at different ages, showing not only the evolution of ossification centres in the carpal bones but also the slowly changing pattern of the individual bones of the hand as well as the distal ends of the radius and ulna. In this way one can compare skeletal maturation in the tubular bones of the hand, the radius and the ulna (all sites frequently affected by diaphysial aclasis), with the carpal bones, which are

very rarely affected by exostoses.

In plotting the height distribution of these patients standard graphs have been constructed using Tanner's (1958)(137) data for normals up to the age of 18, and Kemsley's (1950)(85) figures for normal adults (British population). The problems involved in obtaining normal standards have been discussed at length by Tanner (1958) and will not be repeated here. Although Tanner's and Kemsley's figures for normal adolescents do not coincide, it was decided to show these measurements as a single broken graph rather than as two separate graphs.

Much more difficult to obtain were normal figures for span, symphysial height ("lower measurement") and symphysis-to-vertex ("upper measurement"). Yet it is important to present these figures - and particularly the comparative upper and lower measurements - because they are an indication of the extent to which limb length is affected by comparison with the trunk. The most reliable standards (though unfortunately presented only as mean values) were those of Engelbach (1932), and they are the ones used in this study.(43).

Finally, in order to minimise the possible errors due to using standards which differ from each other as to population measured and the time of these measurements, a comparable series of "healthy" out-patients attending the Royal National Orthopaedic Hospital were measured as well and checked against the standards used.

NORMAL BONE GROWTH.

The early stages in the normal development of human bones was observed in sections obtained from foetal material. Post-natal bone growth was studied in autopsy specimens, the selected sites being the distal end of the femur, the proximal end of the tibia and the bones of the tarsus and foot.

In attempting to evaluate the various theories on the pathogenesis of multiple exostosis it became evident that very little had been written about the normal pattern of transverse growth (as distinct from longitudinal growth) at the epiphysial plates of tubular bones. An attempt was therefore made to reconstruct this process.

Experiments on Rabbits - Radioactive sulphur (S^{35}) in the form of sodium sulphate has been extensively used in the study of cartilage, where it is selectively taken up in the chondrocytes and later in the ground substance as chondroitin sulphate (16). Dziewiatkowski (1952) (39) has shown that the radio-isotope is retained in the cartilage for several weeks and can be detected there by appropriate autoradiographic techniques. Belanger (1954) (8) and Engfeldt and Westerborn (1960) (44) have studied these effects in epiphysial cartilage particularly and have shown that the autoradiographic blackening is most dense in the proliferative and hypertrophic zones of the epiphysial plate.

Similar studies were carried out by the author in

young growing rabbits in an attempt to "label" the cells of the epiphysial plate and observe whether any new, unlabelled cells were added to the periphery of the plate over a period of two to ten days.

Twenty-eight-day old rabbits were injected with S^{35} (0.5 millicurie per 100 G. of body weight) and then killed with intravenous Nembutal at 24 hours, 2 days, 4 days, 7 days and 10 days. The proximal end of the tibia was removed, fixed in formalin, decalcified and embedded in paraffin. Sections through the epiphysial plate were cut and autoradiographs prepared by the stripping film technique described by Pelc (1956)(116

Human Material - Fourteen specimens of the distal end of the human femur were obtained at autopsy from previously healthy individuals who had died in accidents; their ages ranged from six months to 18 years. The bone was split in the sagittal plane and rectangular blocks 0.5 cm. thick were cut from the edge of the raw surface to include the most peripheral part of the epiphysial plate (Fig.9). These undecalcified sections were embedded

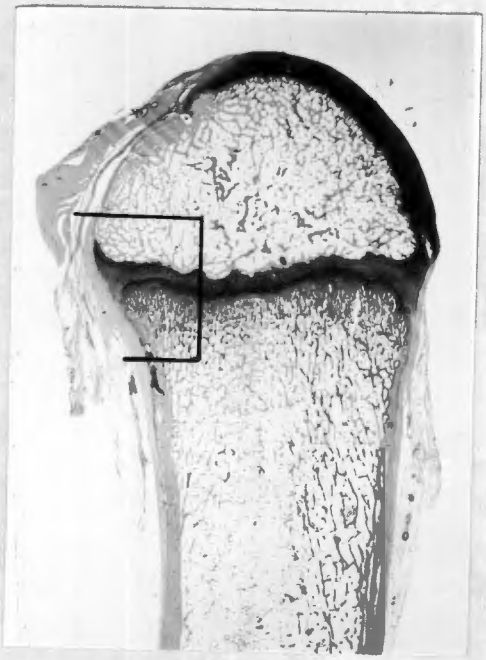

FIG. 9

Section of distal end of femur showing the area studied by microradiography.

in methyl methacrylate, cut to a thickness of 100μ with a circular saw and subjected to microradiography. The method has been described in detail by Jowsey(80) and by Sissons, Jowsey and Stewart (129).

The contact microradiographs obtained in this way were examined for the presence of periosteal bone cuffs or other calcified tissue at the peripheri of the epiphysial plates. Slices of bone were also taken from the adjacent surface, decalcified, sectioned and stained with haematoxylin and eosin prior to microscopic examination.

PATHOLOGY.

Twenty-four specimens of cartilage-capped exostoses, obtained at operation, were available for morbid anatomical and microscopic study. Some of these had already been decalcified and sectioned when first seen. During the period of this study, whenever exostectomy was called for the pathological lesion was removed together with the adjacent, normal cortex. After careful examination the specimen was cut by saw in the vertical plane, showing the exostosis in continuity with the diaphysial cortex from which it arose. A thin slab was taken from the cut surface and radiographed in the undecalcified state ("slab radiography"). The rest of the specimen was decalcified, embedded in celloidin, cut and stained with haematoxylin and eosin.

ESTIMATION OF URINARY ACID MUCOPOLYSACCHARIDE EXCRETION.

Urinary excretion of acid mucopolysaccharide (AMPS) is known to be altered in certain connective tissue disorders, including Hurler's Syndrome (138) and multiple exostosis (102). Urinary acid mucopolysaccharide was estimated in 11 patients of the present series, using the method of Di Ferrante and Rich (1956)(33).

The normal standards of Teller, Burke, Rosevear and McKenzie (1962) (138) were employed. As an additional check, urinary AMPS was estimated in 42 children of various ages with minor orthopaedic complaints attending the Royal National Orthopaedic Hospital. These values corresponded with those of the standards used.

At first, 24-hour specimens of urine were obtained, but this was found to be unnecessary if the values were recorded as the ratio of AMPS to creatinine in any single specimen of urine. This greatly facilitated the use of the method which was later extended to a study of cartilaginous tumours in general.

PART II

CLINICAL, RADIOLOGICAL AND MORBID ANATOMICAL ASPECTS OF HEREDITARY MULTIPLE EXOSTOSIS.

C H A P T E R IV.

INCIDENCE OF HEREDITARY MULTIPLE EXOSTOSIS.

A. FREQUENCY.

The frequency of hereditary multiple exostosis is unknown and cannot be estimated with any degree of accuracy from the available data. Krooth, Macklin and Hilbish (1961) (87) studied this condition in a relatively closed community among the Chamorros on the Pacific island of Guam. They discovered 21 cases in a population of 32,000 Chamorros and estimated that this represented more than 50 per cent of the cases on the island, giving an incidence of approximately 1:1000.

The same authors quote Dr. E.B.D. Neuhauser's estimate of one new case per year at the Children's Medical Centre, Boston, which handles 90,000 out-patients annually.

It is estimated that three new cases are diagnosed each year at the Royal National Orthopaedic Hospital, which specialises in orthopaedic diseases and handles approximately 7000 new patients annually.

Both Jaffe (1958) (77) and Lichtenstein (1952) (100) regard multiple exostosis as "the most common of the systematized anomalies of skeletal development." Unlike

some of the other generalised skeletal abnormalities (such as achondroplasia, or osteogenesis imperfecta) this disease is not inherently lethal; considering the genetic pattern, the incidence may therefore be expected to be maintained in successive generations.

B. AGE.

Stocks and Barrington (1925) (135) extracted the following data from over 1,000 cases of multiple exostosis reported in the literature:

5 - 6 per cent were noticed during the first year of life.
16.5 per cent were noticed during the first two years of life.
31-33 per cent were noticed in the third-fifth years of life.
24-25 per cent were noticed in the sixth-tenth years of life.
2.75 per cent were noticed after the twentieth year.

There is no disagreement about the fact that this is a disease of childhood and adolescence. (30; 46; 77; 100).

The age distribution (i.e. the age at which the disease was first encountered) in the present series is illustrated in Fig. 10.

An analysis of this sort, however, gives no indication of the age of onset of the disease. Indeed, it is likely that the basic abnormality is always present in the embryo and might be detected at birth by radiographic examination.

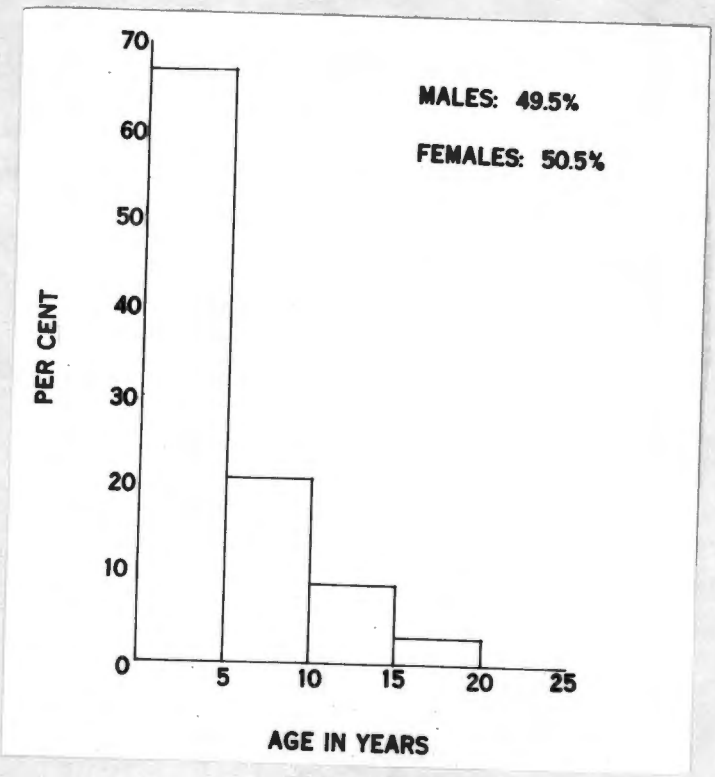

FIG. 10

Age and sex distribution of multiple exostosis in fifty-two index patients and twenty-four relatives. Histogram shows age at which first discovered.

C. SEX.

Of the 1,124 cases of multiple exostosis from the medical literature, analysed by Stocks and Barrington in the Treasury of Human Inheritance (1925) (135) the sex was recorded in 1,028. Of these, 716 were males and 312 females, giving a sex ratio of 69.66 per cent. In 727 of the reported cases there was a family history of multiple exostosis; the sex ratio of this group was the same as that for the cases without a clear hereditary tendency! Ehrenfried's 236 cases (40; 41) are not analysed separately, as they were included in Stocks and Barrington's figures.

These findings appeared at the time to be irrefutable and have gradually become entrenched in the description of the disease. However, a close examination of their original sources (particularly those dating back prior to the development of radiography) raises considerable doubt about the validity of their figures. This is most important in the interpretation of the genetic implications of their findings and the matter is discussed in greater detail in the section on Heredity.

A study of the literature since 1925 shows a marked variation from Stocks and Barrington's figures. The more important authors are listed in Table I.

TABLE I

SEX DISTRIBUTION OF MULTIPLE EXOSTOSIS. CASE REPORTS IN THE LITERATURE.

AUTHOR	Number of cases reported	Ratio of males : females
Eriksson & Fredbarj (1935)	24	1:1
Vanzant & Vanzant (1942)	230	3:2
Jaffe (1943)	28	7:3
Lichtenstein (1952)	- - -	1:1
Dahlin (1957)	272	3:2
Krooth et al. (1961)	21	3:4

The sex ratio in these groups averages out at 55 per cent (males: females).

In the present series, the findings were as follows :

Of the 52 index patients examined radiologically, 27 were males and 25 were females.

Of the 88 secondary cases, 43 were males and 45 were females.

A detailed analysis of the sex relationships is presented in the section on Heredity.

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C H A P T E R V.

CLINICAL PRESENTATION.

The name hereditary multiple exostosis - preferred by some people for its descriptive simplicity avoiding any reference to the basic pathology, as yet unknown, but hinted at in the term diaphysial aclasis - conveys at least two important features of the disease. It is a heritable disorder of the skeletal system; its most striking manifestations are the numerous cartilage-capped exostoses which appear in different parts of the skeleton. The picture is completed by certain characteristic deformities resulting from deficient growth of the bones involved.

Over eighty per cent of the patients are discovered in the first decade of life, males and females being affected with equal frequency (Fig. 10). In fact, the earliest lesions may be present at birth and are occasionally detected soon after by the searching hands of a parent herself afflicted by the disease. The mere presence of a bony lump, coupled with the knowledge that the disease is "in the family", is sufficient reason for seeking medical advice in the vast majority of cases.

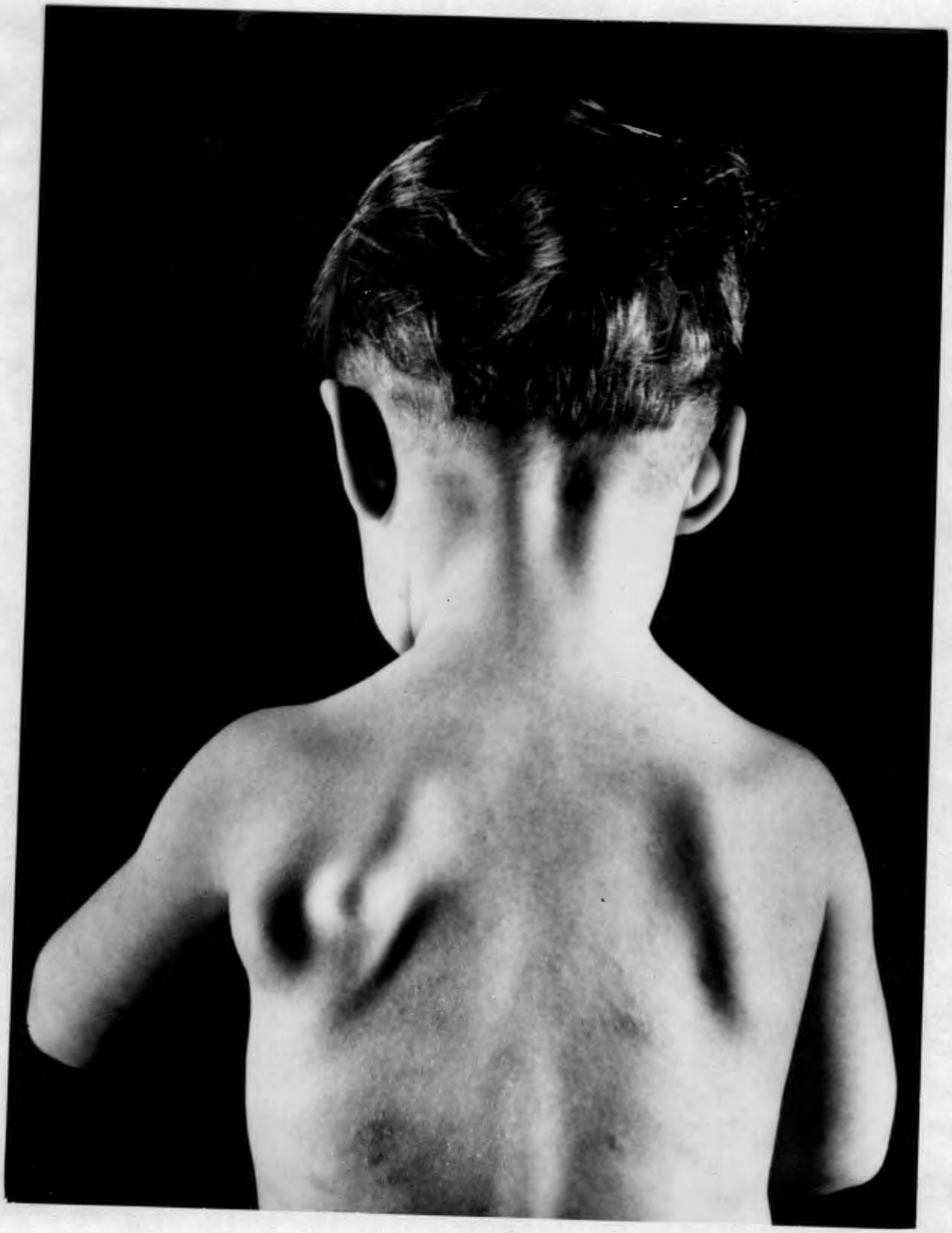


FIG. 11

Exostosis of the left scapula first discovered at the age of one year.

TABLE II

REASONS FOR SEEKING ADVICE

	Number of Cases
1. Cosmetic	44
2. Accidental Discovery	11
3. Pain	8
4. Deformity	7
5. Impaired Function	5
6. Pressure Effects	1
TOTAL	76

New mutants, on the other hand, are sometimes discovered accidentally in the course of investigating some other illness. Occasionally it is one of the secondary deformities or the effects of pressure by an exostosis that first call attention to the disease. Doubtless, too, some are affected so mildly as to remain unaware of their abnormality throughout life. (See Table II).

Lesions of the tibia and scapula are usually discovered first, simply because they are the most conspicuous sites in the child (Fig. 11). A radiograph at this stage invariably shows early exostoses in many of the other bones as well. Soon these become palpable and visible as the picture of a generalised skeletal disorder unfolds. During the years of rapid growth the exostoses enlarge and pain in one or other of the lesions is common throughout this period. It is seldom that a child reaches the end of the growth period without consulting a doctor about his abnormality.

The patient in a full-blown case presents a characteristic appearance (Figs. 12 and 13). Innumerable bony lumps may be seen and palpated as they jut into the soft tissues around the more actively growing parts of the endochondral skeleton. Juxta-epiphysial in origin, they are found typically at the ends of the tubular bones,

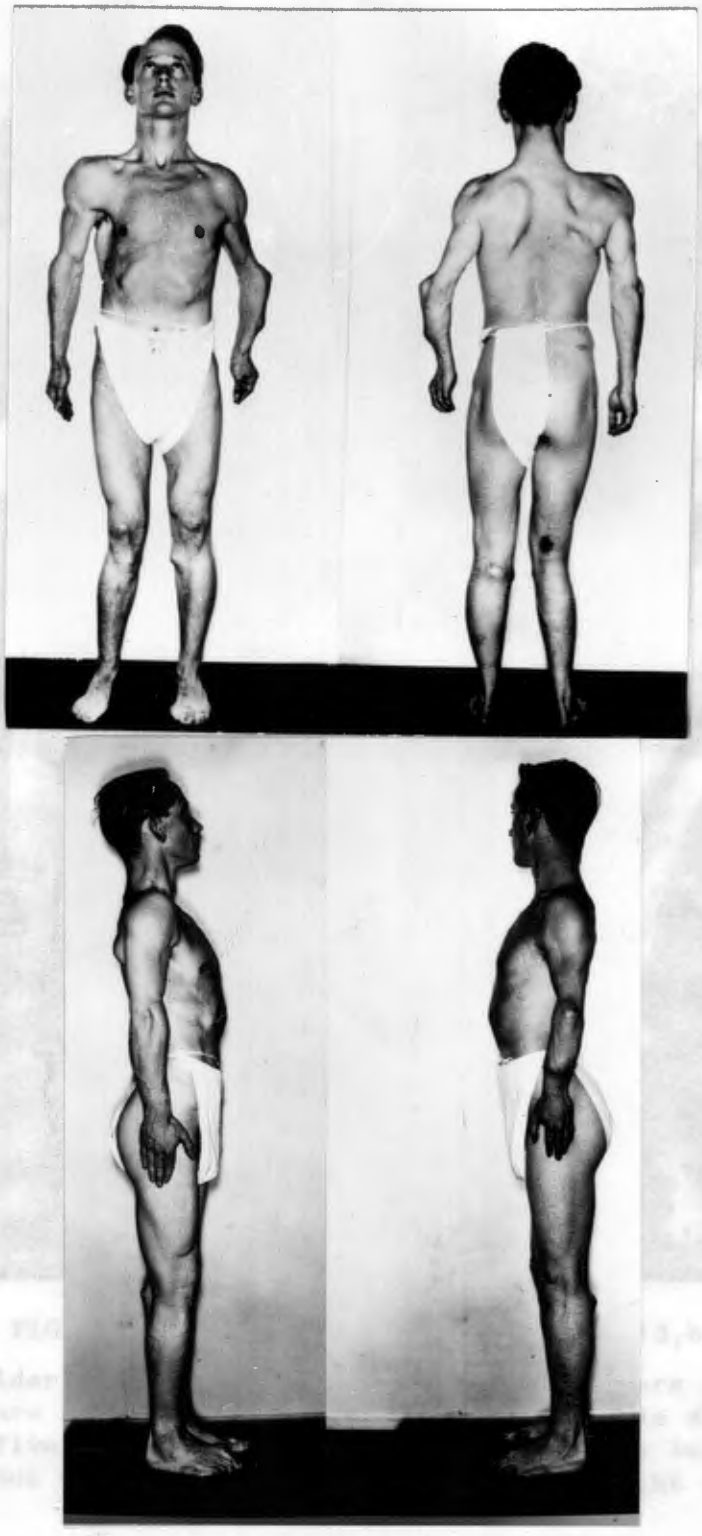
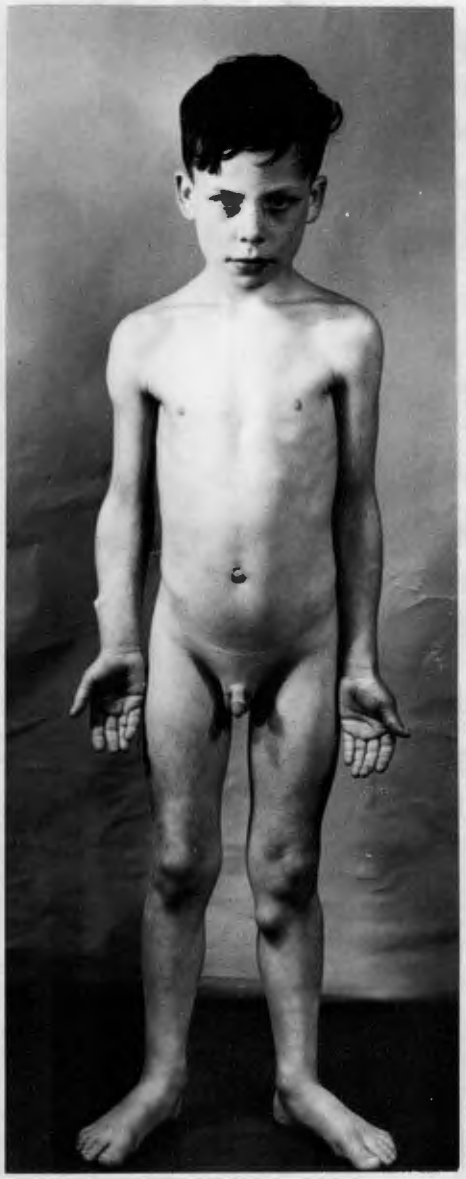


FIG. 12

Patient showing all the features of hereditary multiple exostosis. Note particularly the juxta-epiphysial swellings and the deformities of the forearm, knee and ankle. (Patient charted in Pedigree No. 3; II, 3).



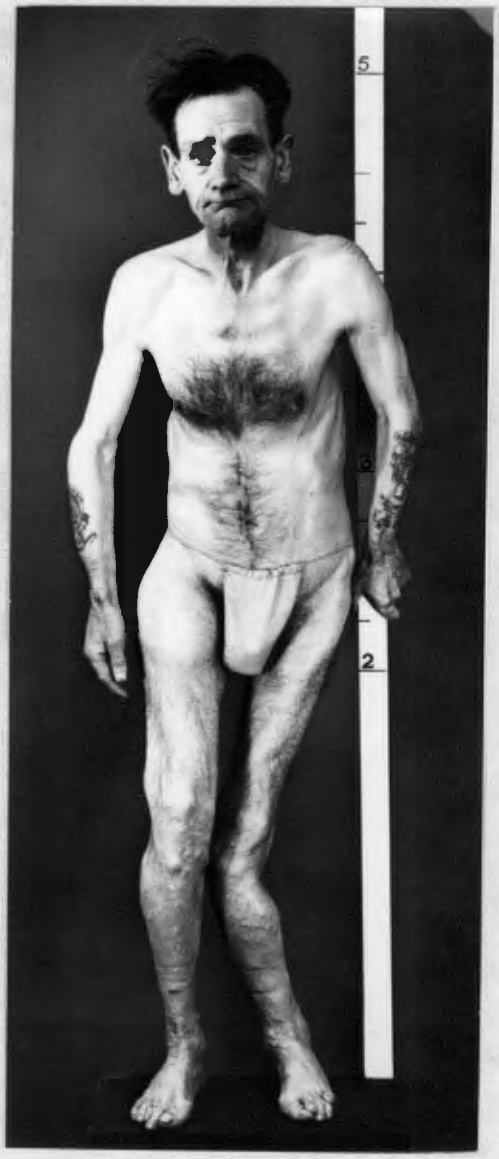


FIG. 13,a FIG..13,b

Young and elderly patients contrasted. At five years (Fig. 13,a) exostoses are clearly visible but there is little deformity. At sixty-five years the patient in Fig. 13,b has less obvious exostoses but the abnormality of growth has wrought its effect and caused severe deformities.

the vertebral borders of the scapulae, the iliac crests and ribs. However, any of the endochondral bones may be involved.

Bone growth, too, is affected, giving rise to recognisable deformities in approximately three out of every four of these subjects (Table XI). The commonest are a shortness of stature, bowing of the radius with ulnar deviation of the wrist, subluxation of the radio-humeral joint, valgus deformity of the knee and ankle, tibio-fibular synostosis and asymmetry of the pectoral and pelvic girdles. Of these, only the ankle deformity is usually bilateral and symmetrical; the others occur in haphazard association, but none ever in the absence of associated exostoses. These deformities and their pathogenesis are described in detail in the section on Bone Growth in Multiple Exostosis in Part III. Here, too, the evolution of the exostoses and their peculiar distribution are more fully discussed and related to the differences in bone growth at the various sites.

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C H A P T E R VI.

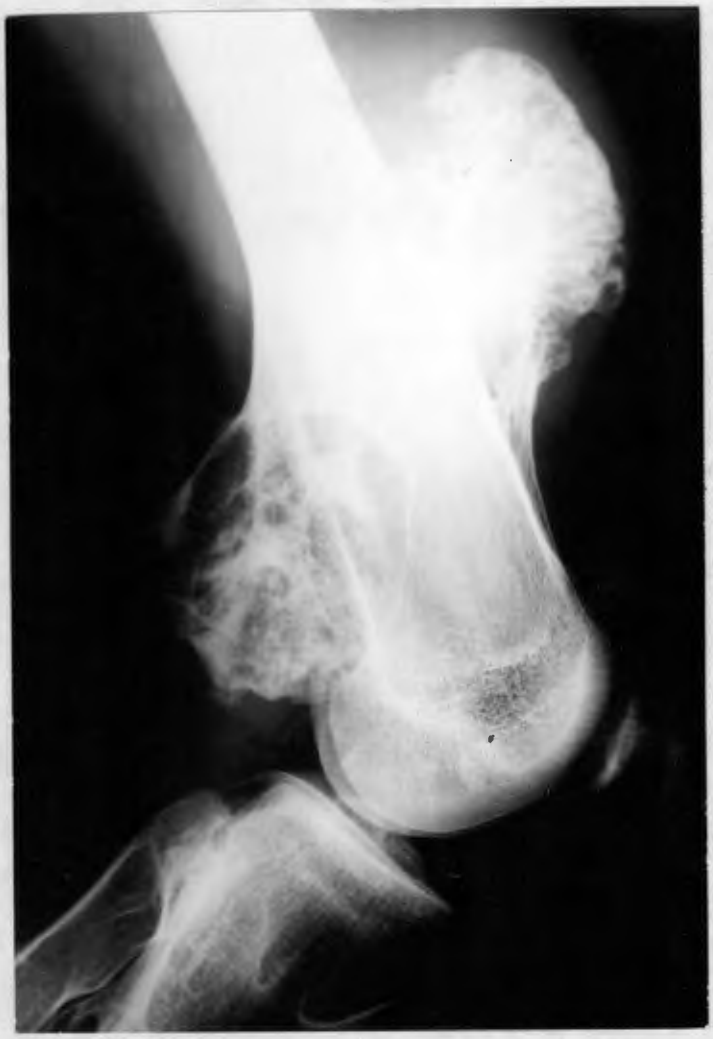
RADIOLOGICAL FEATURES.

The lesions of multiple exostosis can be demonstrated in over 95 per cent of cases by a single radiograph of the bones articulating at the knee joint. Other characteristic sites are the distal ends of the tibia and fibula, the proximal end of the femur, the distal ends of the radius and ulna, the proximal end of the humerus, the scapula, the pelvis, the clavicle and the bones of the hand and foot (Fig. 14). Any of the endochondral bones may be affected, however, including the bones around the elbow, the vertebrae, the tarsus and the carpus (Fig. 15).

The radiographic lesions in the full-blown case are predominantly metaphysial, In the tubular bones this region is usually expanded or irregularly club-shaped, with numerous exostoses jutting from the bone. They vary in size from a minute spike (a common lesion on the smaller bones of the hand and foot) to a cauliflower-like mass on the larger bones. Some appear to be sessile, others are stalked or sometimes tapered to a long, thin process. Where the bony cortex can be traced throughout, it is seen to be continuous with the exostostotic lesion, enclosing a cancellous sponge-work which is likewise

FIG. 14

Radiographs showing some of the more common lesions in multiple exostosis. a) Distal femur, proximal tibia and fibula; b) hands; c) feet; d) humeri, ribs; e) scapula; f) clavicle.

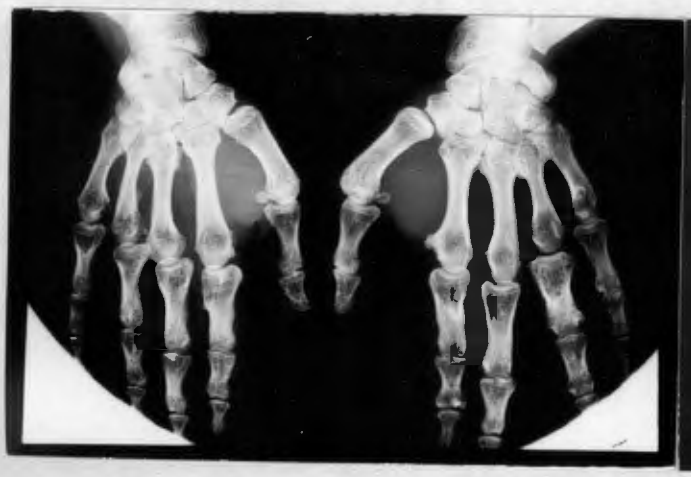


(a)

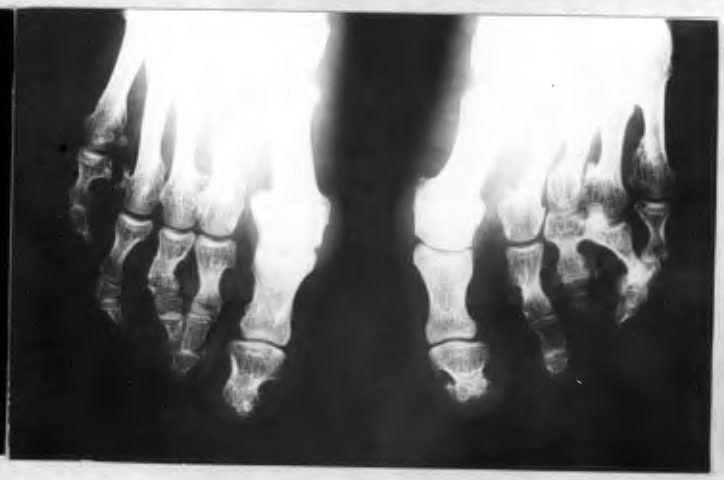
Note the variety in the form of the exostoses. In each case, however, the lesion is continuous with the structure of the bone from which it arises. In the scapula the vertebral border is, itself, almost entirely 'exostotic'.

The exostosis at the acromial end of the clavicle was the lesion commonly encountered in this bone, unlike the small, pearly exostoses described by Jaffe.

In the hands and feet exostoses occurred frequently at the non-epiphysial ends of the tubular bones.

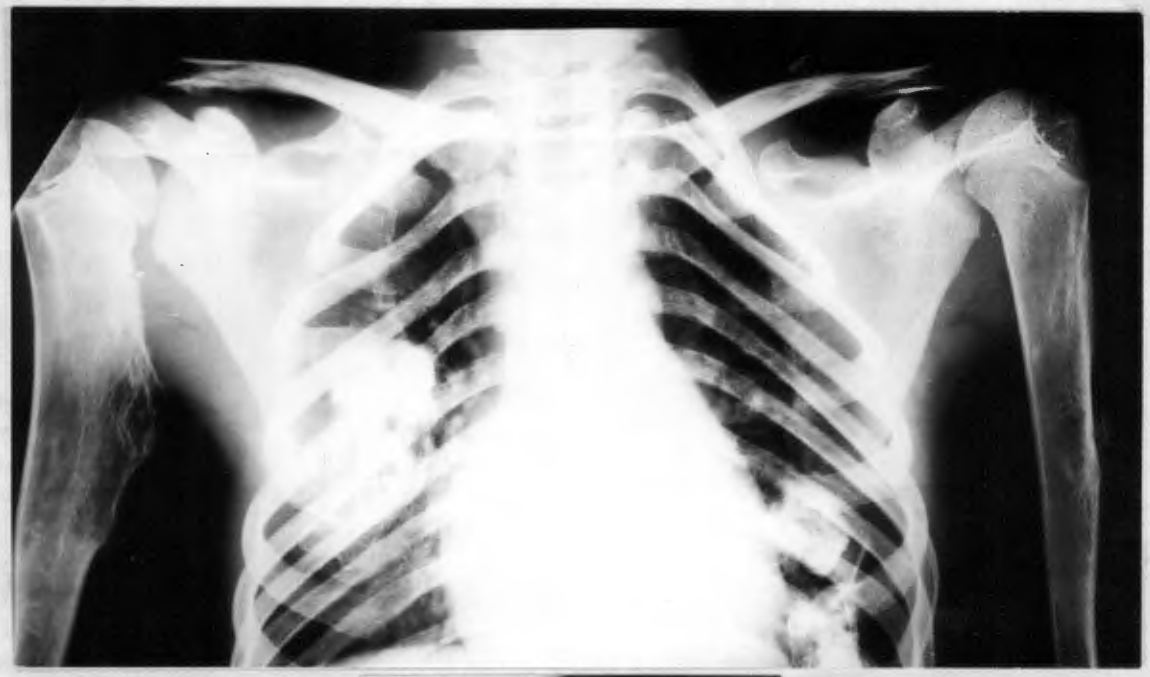


(b)

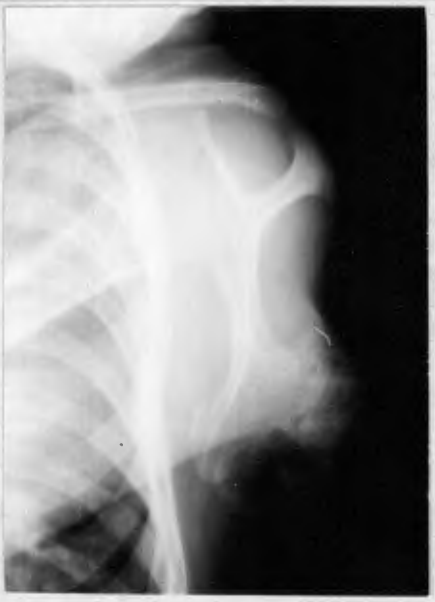


(c)

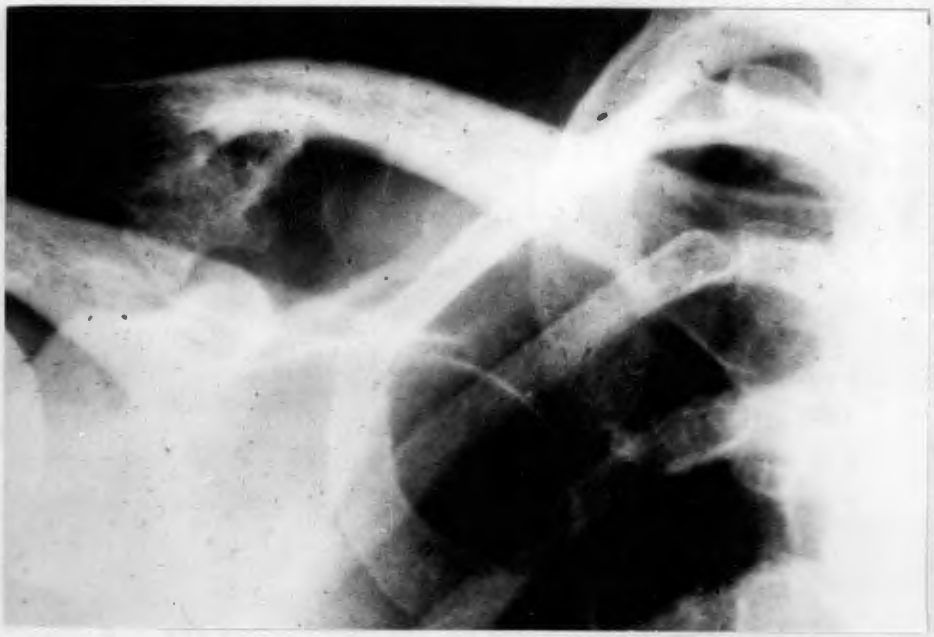
FIG. 14



(d)



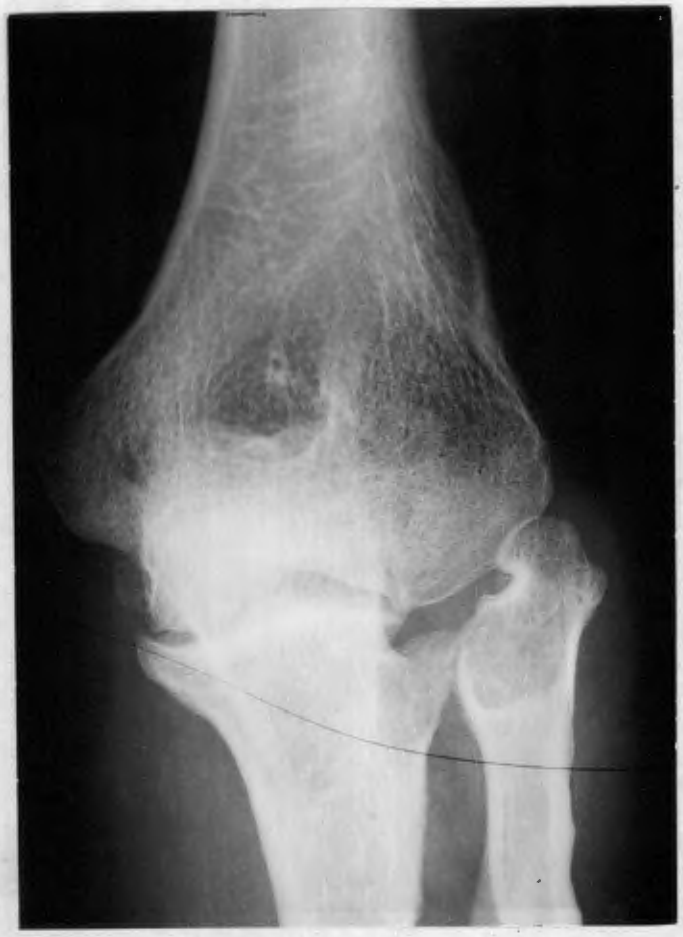
(e)



(f)

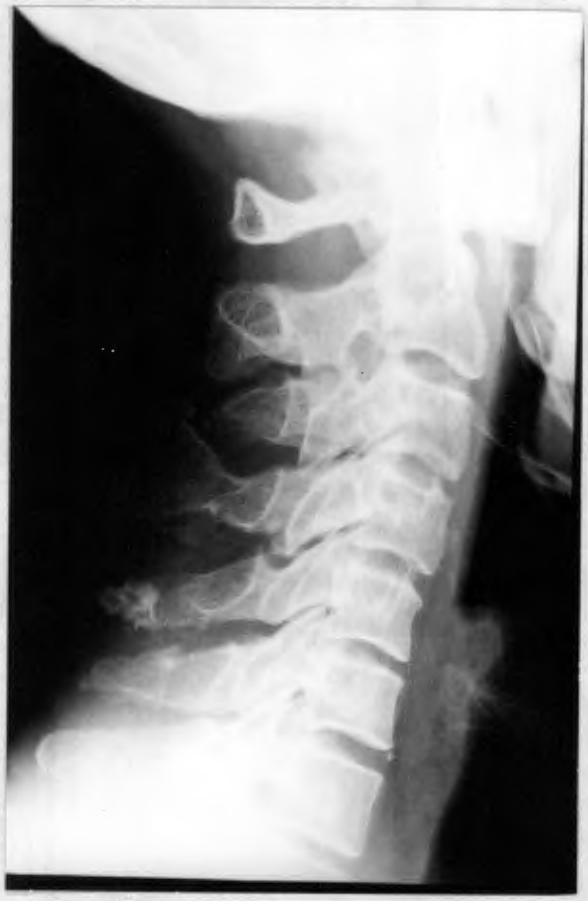
FIG. 15

Radiographs of a) distal humerus, proximal radius and ulna; b) cervical spine; c) tarsus and d) carpus. These sites are seldom found affected in the adult but exostoses or distorted growth of bone occur quite often at some stage during early development.



(a)

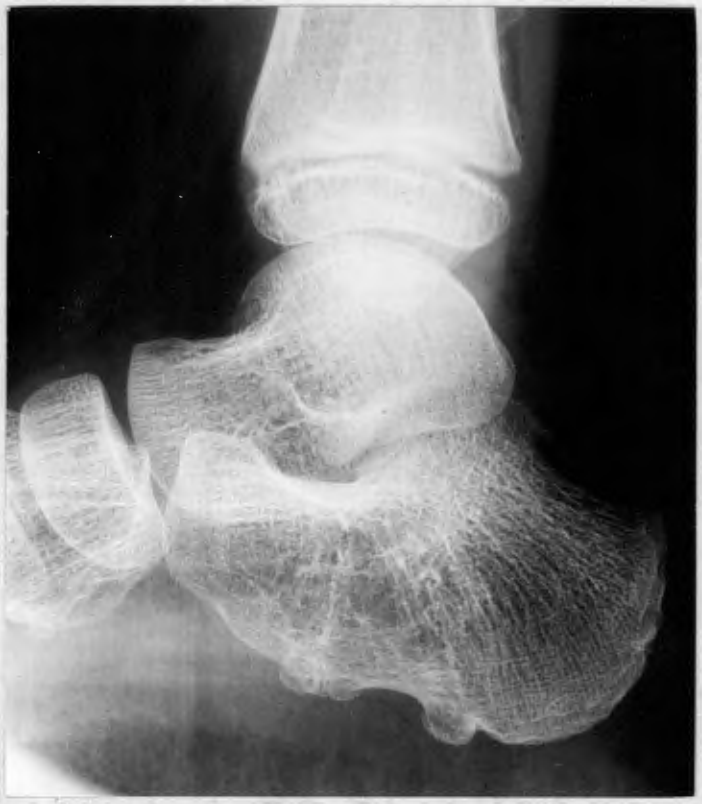
Exostosis and slight thickening of the distal end of the humerus. Note the distorted growth and subluxation of the proximal end of the radius.



(b)

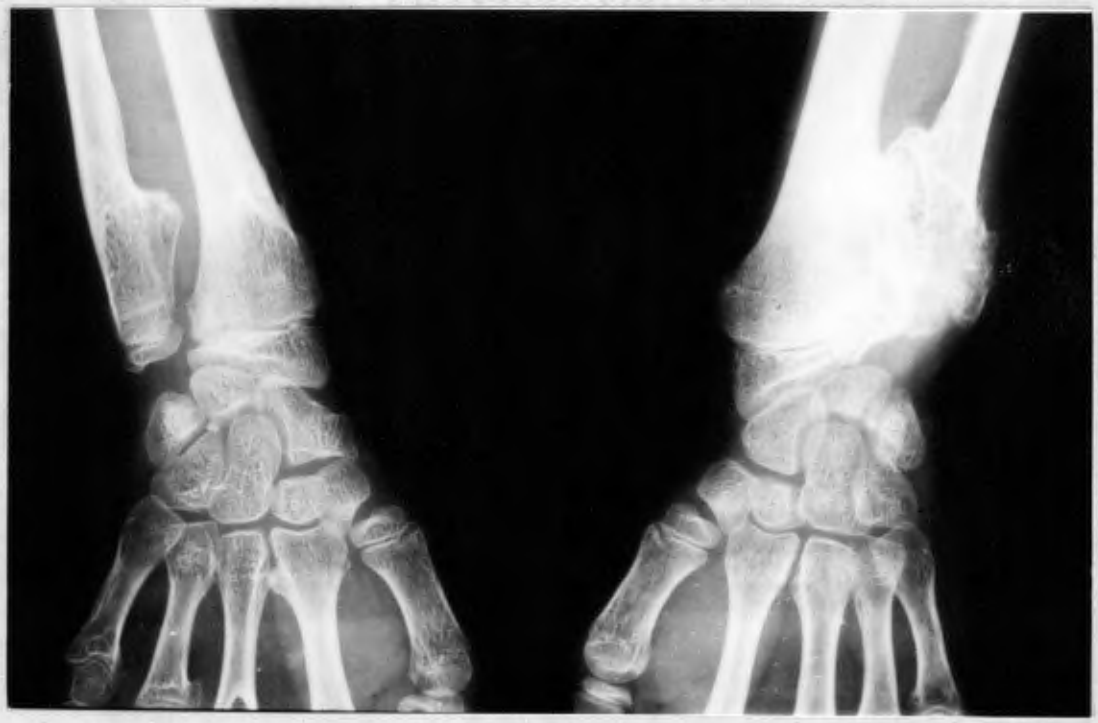
Exostoses of the vertebrae almost invariably occur on the elongated processes and are related to epiphysial growth.

FIG. 15



(c)

Exostoses of the calcaneum



(d)

Comparison of the right and left scaphoid shows the deformity of this bone in the right wrist.

continuous with the spongy bone of the metaphysis. Viewed end-on, and particularly in a large, sessile exostosis, this peripheral cortex enclosing a less dense, central area, may resemble an enchondroma and has often been mistaken for such (Fig. 18). True enchondromata or central, expanding lesions are not seen in hereditary multiple exostosis.

A frequent appearance in any large exostosis, and one which sometimes occasions undue alarm, is a patchy density of the tumour mass due to calcification in the cartilage cap surmounting the exostosis (Figs. 16 and 19). This may indicate a tumour of enormous size, suggesting the possibility of malignant change. However, unlike a chondrosarcoma, there is a uniformity in the pattern of calcification and the limits of the calcified area can be clearly and unequivocally traced at every point on the radiograph.

In addition to the exostoses, certain characteristic deformities are well illustrated radiographically. The commonest of these is bowing of the radius and tapering of the distal end of the ulna (Fig. 51). The radiohumeral joint may be subluxated or dislocated (Fig.52). Valgus deformities at the knee and ankle are equally well demonstrated (Figs. 53 and 54).

Similar deformities are seen in dyschondroplasia

or Ollier's disease but the associated features of this condition make it easy to distinguish from diaphysial aclasis.

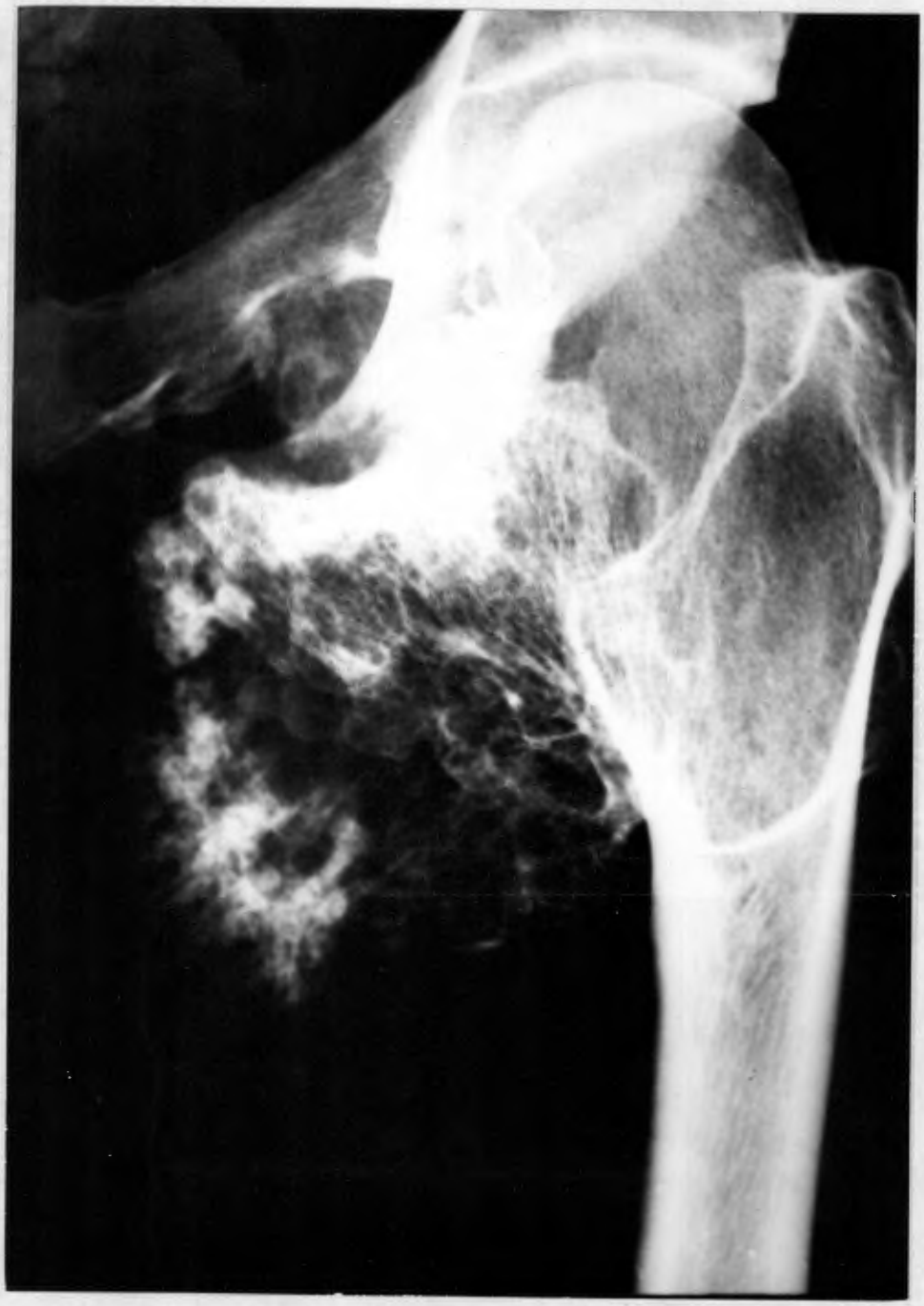


FIG. 16

Radiograph of a large exostosis of the proximal end of the femur, with patchy calcification in the cartilage cap.

C H A P T E R VII.

DIFFERENTIAL DIAGNOSIS.

DYSCHONDROPLASIA.

The one condition which has persistently been confused with hereditary multiple exostosis is dyschondroplasia or multiple enchondromatosis. This was described as a distinct entity by Ollier (111) in 1900 but, following the teaching of Virchow (145) most writers of the 19th and early 20th centuries made little distinction between hereditary multiple exostosis and enchondromatosis (dyschondroplasia)(3; 5; 15; 25; 27; 29; 72; 74; 108; 143).

For example, Ehrenfried, (1917) (41) , one of the most important of the early American writers on this subject, stated (Case 1): "Both ilia show a peculiar series of radiating striations about the crests;"and (Case 2): "The upper ends of the humeri show irregular enlargement .....with longitudinal striation. The metacarpals and phalanges show irregular enlargement and vacuolation ....."; and again (Case 3): "The shoulders show the characteristic striated elongation of the upper end of the humerus .....The fingers show globular enlargement at the metacarpo-phalangeal articulations and the first interphalangeal articulations." (None of these three patients gave a family history of exostosis.) These are, in fact the radiological signs of dyschondroplasia.

Similar errors, either in observation or in nomenclature, occur in many of the older case descriptions of multiple exostosis. Indeed, Stocks and Barrington (135) in their review of the literature, were led to conclude that "enchondromata may occur in some members of a family and exostoses in others, and any kind of admixture of the two disorders in families or cross-inheritance between them seems to be possible."

Although there are superficial similarities, particularly in the deformities of the forearms and ankles, it is now well known that these are two separate and distinct conditions with different clinical, radiological and genetic features. (46; 77).

In multiple exostosis there is usually a family history; in dyschondroplasia never. The bony spurs or exostoses that do occur in dyschondroplasia are small and few in number; they are the least significant feature of a well recognised radiological pattern, which appears characteristically as a radiolucent streaking of the metaphysial region, due to retained columns of cartilage extending longitudinally from the epiphysial plate into the diaphysis (Fig. 17). Central enchondromata are also common, particularly in the metacarpal bones and phalanges.

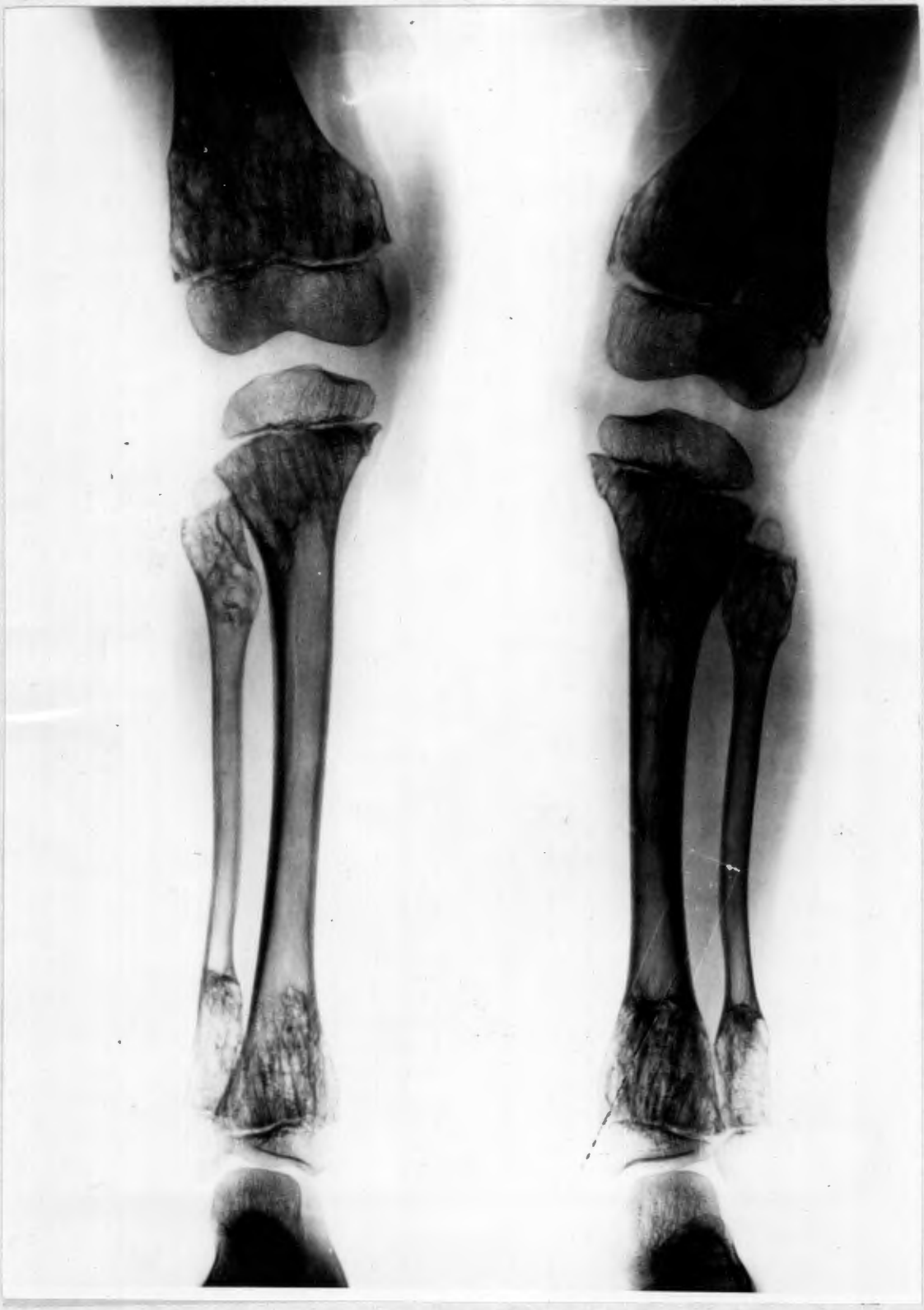


FIG. 17

The radiographic features of dyschondroplasia. The longitudinal streaking in the metaphysial regions is due to retained columns of unossified cartilage.

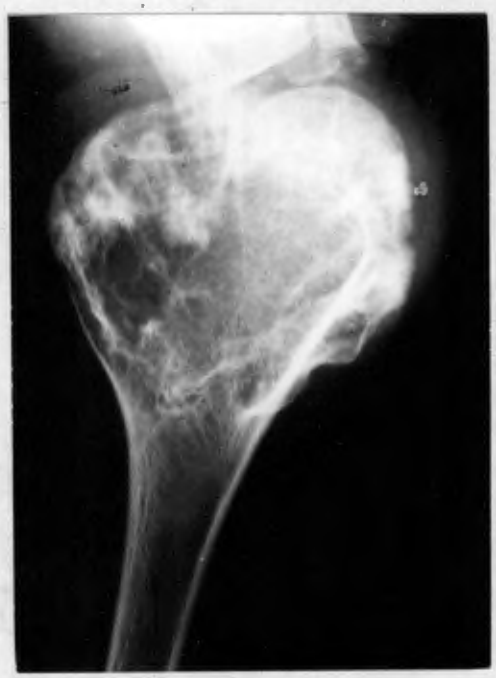


FIG. 18

Radiograph of a sessile exostosis, projected end-on, giving the appearance of an enchondroma. This is the same exostosis as that shown in Fig. 46.

Fig. 18 shows what has often been mistaken for an enchondroma in a case of multiple exostosis. This appearance is due to the radiographic projectian giving an end-on view of a large sessile exostosis. Central, expanding chondromata do not occur in hereditary multiple exostosis.

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C H A P T E R VIII.

PATHOLOGY.

The characteristic lesion in multiple exostosis is not, in fact, the pedunculated cortical exostosis (though this is often seen as well) but rather a diffuse, club - shaped thickening of the metaphysis, irregular in outline, heaped and cleft by innumerable bony excrescences or sessile exostoses. One or more of these may enlarge and project as a pedunculated mass, sometimes smooth in outline, sometimes cauliflower-like and of frightening dimension. (Fig. 19).

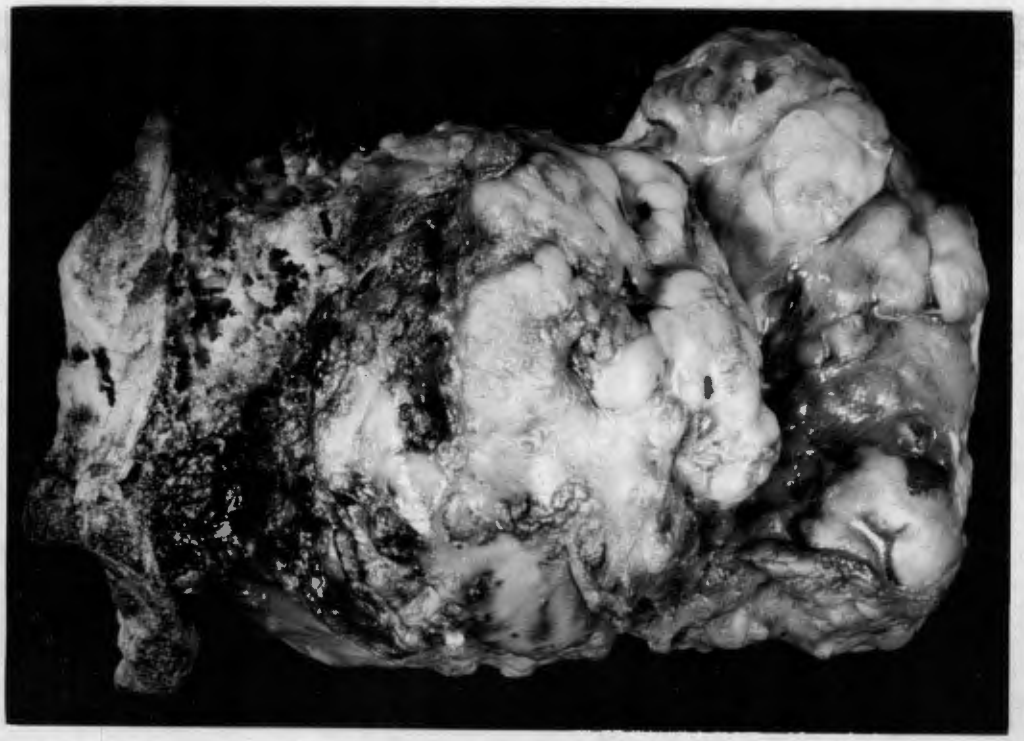
Glistening and pearly white, the lobular mass is enveloped in a periosteal membrane continuous with the periosteum of the parent bone. It is closely applied to the underlying tissue, ensheathing the numerous excrescences and dipping into the clefts between them.

Larger in size than the radiograph would suggest, the outer part of the mass consists of a cartilaginous covering or cap which surmounts the bony projection. A saw-cut at right angles to the parent bone shows this to best advantage (Fig. 20). During the period of growth the cartilage cap is sometimes 0.5 - 1.0 cm. in thickness, and seldom less than 2 mm. After the cessation of growth most of the cartilage ossifies and the cap is thinned to a narrow lining which may be entirely absent in many places. Sometimes, however, it persists into adult life and may even increase in size.

FIG. 19

(a) A densely calcified exostosis obscuring the left scapula in the radiograph.

(a)



(b) The large, lobulated tumour excised with the vertebral border of the scapula.

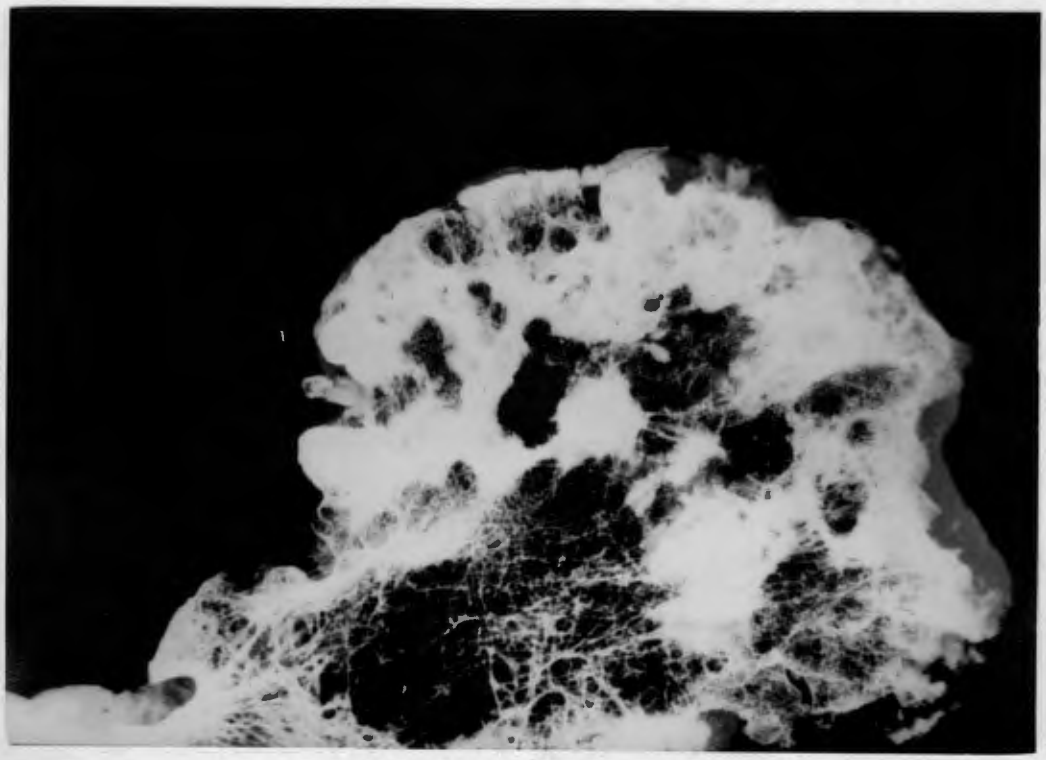
(b)

FIG. 20, a & b

(a) Slab radiograph of the proximal end of the femur showing multiple exostoses continuous with the parent bone.

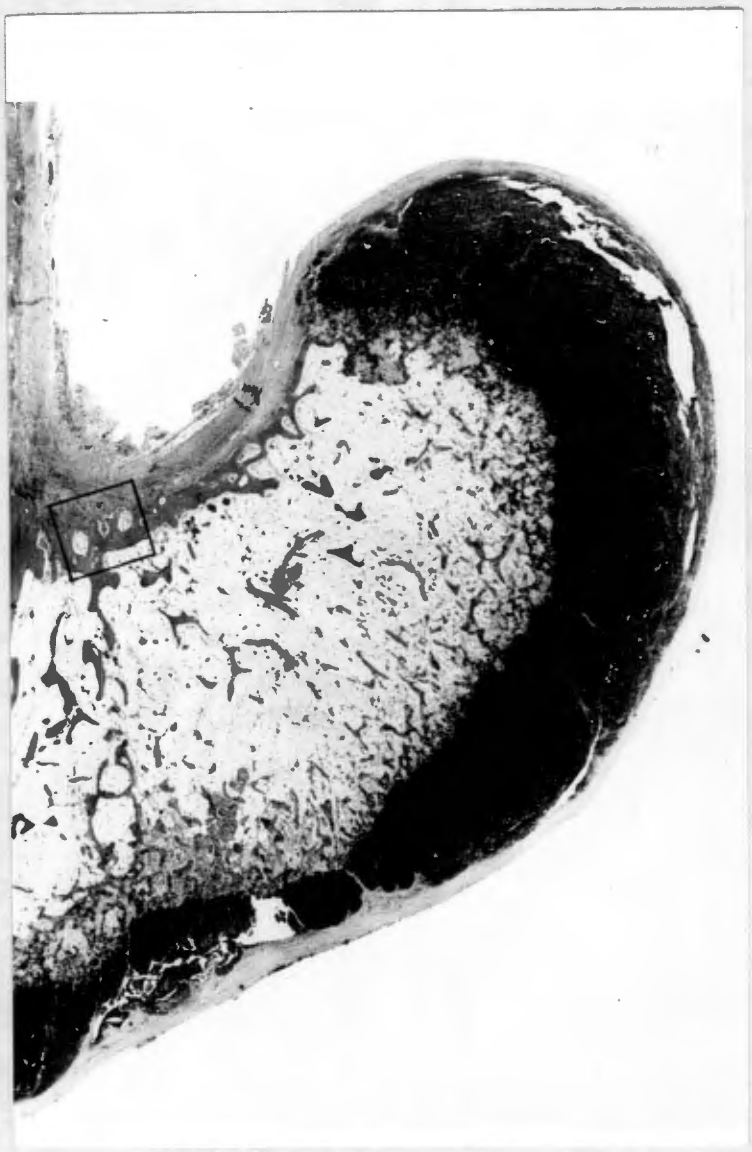
(b) Slab radiograph of an exostosis showing bony trabeculae at the base and neck and densely radio-opaque calcification in the cap.

(a)



(b)

FIG. 20,c.



Low-power view of a cartilage-capped exostosis. The darkly staining cartilage makes up almost one quarter of the bulk of the exostosis. The neck of the lesion is continuous with the bone of the diaphysis. The periosteum, which covers the exostosis throughout, is thick in the region of the neck and thin over the cartilage cap.

In each exostosis is reproduced the structure of the bone from which it arises, an outer cortex and an inner spongiosa with marrow spaces continuous with the medullary cavity of the bone. Thus the exostosis does not sit upon the underlying cortex, but arises in continuity with the parent bone. This is clearly shown in the slab radiographs in Figures 20,a and b and the section in Figure 20,c.

In the larger tumours, and sometimes in the smaller ones, degeneration and calcification of the cartilaginous mass may produce the characteristic radiographic appearance referred to earlier (Figs. 16 and 19). Extensive areas of cartilage may be replaced by the soft, chalky material, small specks or patches of which occur also among the bony trabeculae (Fig.21,a). A slab radiograph of the cut surface shows the trabecular pattern of the exostosis and the dense, calcified areas (Fig.21,b).

Microscopic Features (Figs. 20,c; 22; 23).

The osseous part of the exostosis differs in no way from normal lamellar bone - indeed, is simply a continuation of the parent bone, with a dense cortex and cancellous spongiosa broken up by marrow spaces.

The cap or covering consists of hyaline cartilage, in which the chondroblasts are seen in every stage of maturation. In the more peripheral areas immature forms, including occasional binucleate cells, are observed.

(a)

(b)

FIG. 21, a & b.

Cross section and slab radiograph of the exostosis in Fig. 19.

Towards the osteocartilaginous junction the cells are increasingly mature; here the familiar, columnar arrangement of the epiphysial plate is crudely reproduced and endochondral ossification proceeds slowly and irregularly until the epiphyses join (Fig. 22).

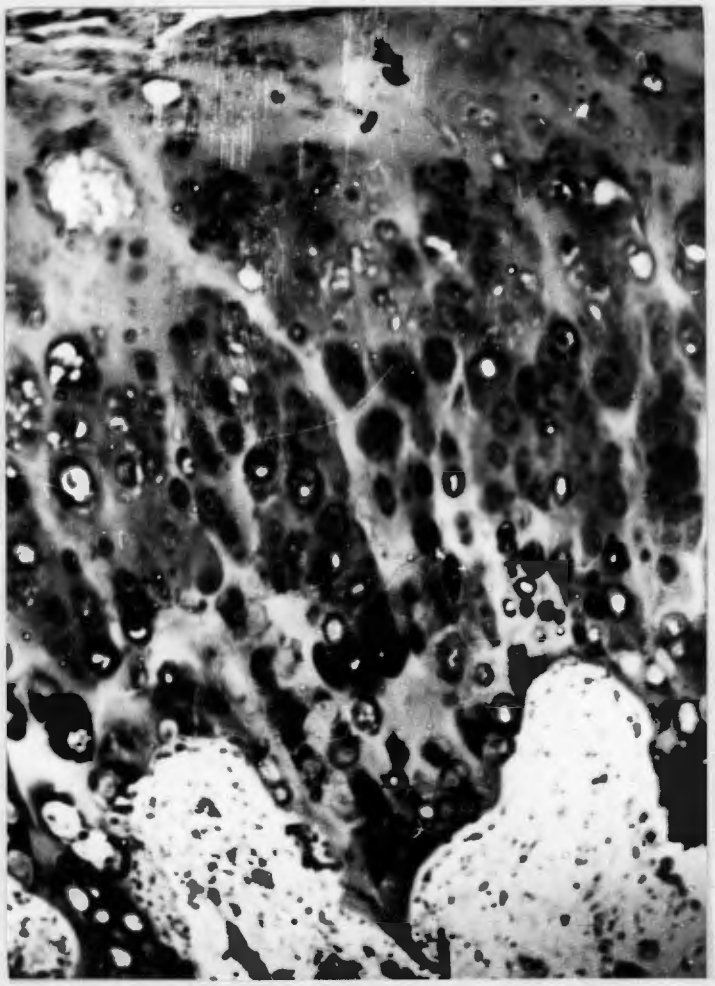


FIG. 22

High-power view of the osteocartilaginous junction in an exostosis. The columnar arrangement of the cartilage cells is reminiscent of the epiphysial plate.

Towards the end of adolescence, and certainly after the cessation of growth, this semblance of organisation and regularity disappears as the cartilage cap involutes and becomes ossified. In the older adult, the exostosis may be almost entirely osseous, with islands of cartilage lying

dormant between the bony trabeculae. In some areas the cartilage tissue may be degenerate and impregnated with calcium detritus. These features are seen in Figure 23.

Occasionally, small groups of cartilage cells are seen in the subperiosteal layer of the exostosis, and even at a distance from the lesion along the diaphysis. It has been adduced that these cells originate from pluripotential periosteal cells and give rise to exostoses (106). However, this phenomenon has not, so far, been described in children and, in the present study, was only seen in specimens obtained from adults where much of the exostosis had been replaced by bone. It appears to the author that these cell clusters may be the remnants of previous cartilaginous exostoses, or else might have originated at an early age with the exostoses, failed to develop further and been separated from the original lesion by elongation of the bone.

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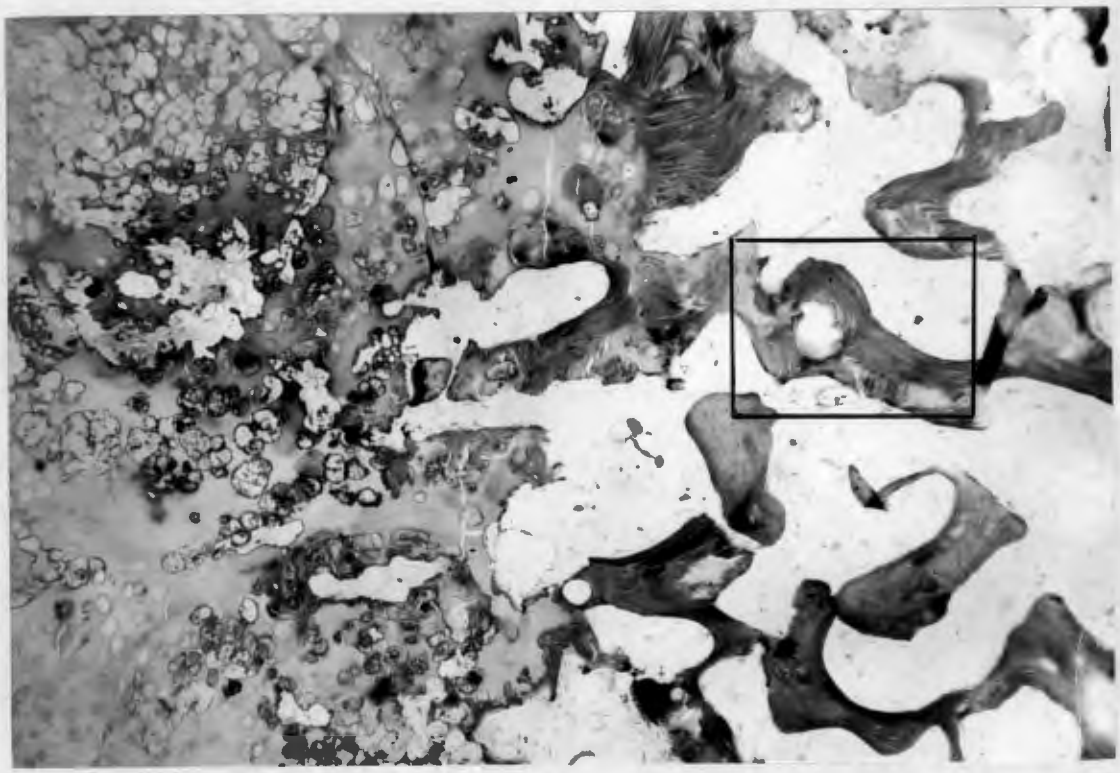
FIG. 23



(a) Photomicrograph of the central part of an exostosis in an adult showing degeneration of the cartilage tissue in the left half of the figure (x 120).

(b) Photomicrograph of the area marked out in (a). Tiny islands of cartilage have been trapped in the bony trabecula and lie dormant there (x 480).

C H A P T E R IX.

COMPLICATIONS.

Some disturbance of functional activity, particularly on careful, objective examination, is so common as to be part of the usual clinical picture of multiple exostosis. Serious disability, however, is seldom met with in the average case.

TABLE III

THE COMPLICATIONS OF HEREDITARY MULTIPLE EXOSTOSIS

COMPLICATIONS	NUMBER OF PATIENTS	
	Index cases (56)	Secondary cases)20)
Interference with function	36	8
Pressure effects	4	1
Fracture of exostosis	2	0
Exostosis bursata	3	1
Chondrosarcoma	0	1

The complications which required medical attention in the present series are presented in Table III. For statistical purposes only the 56 index patients should be

considered. For completeness, however, additional figures are given for another 20 secondary cases examined in sufficient detail both clinically and radiologically.

Interference with Function.

Functional disability, in most cases, is caused by a combination of factors, of which a mechanical restriction of movement is the most important. Sometimes this is due to a large exostosis impinging upon an adjacent bone; the hip and knee suffer most in this respect (Figs. 14 and 16). In others, the associated bony deformities are the limiting factor; supination and pronation of the forearm and movements of the wrist are affected by bowing of the radius and ulnar deviation at the radio-carpal joint (Fig. 51). In one case (Fig. 13,b) marked genu valgum led to instability of the knee and necessitated the use of a caliper. Valgus deformities of the ankles may require treatment. Occasionally exostoses on adjacent fingers embarrass hand movements. Interference with tendons, though hardly ever serious, may call for exostectomy.

Pressure Effects.

Considering the large number of exostoses in each patient it is surprising how seldom they cause pressure upon adjacent structures. In one of the 56 index patients a large pelvic exostosis caused urinary obstruction, renal failure and death; malposition of a pregnant uterus

occurred in another. One patient with a large femoral exostosis had sciatic pain and another with a fibular exostosis developed a peroneal nerve palsy.

Intestinal obstruction (86) and arterial aneurysms (21) due to pressure by exostoses, have been described as well, but were not encountered in the present series. A report (24) of 21 cases of dysphagia due to "exostosis", quoted by Coley (1949), proved to be due to conditions other than hereditary multiple exostosis - which is to be expected, considering that the vertebral bodies do not develop cartilaginous exostoses larger than a few millimetres in diameter.

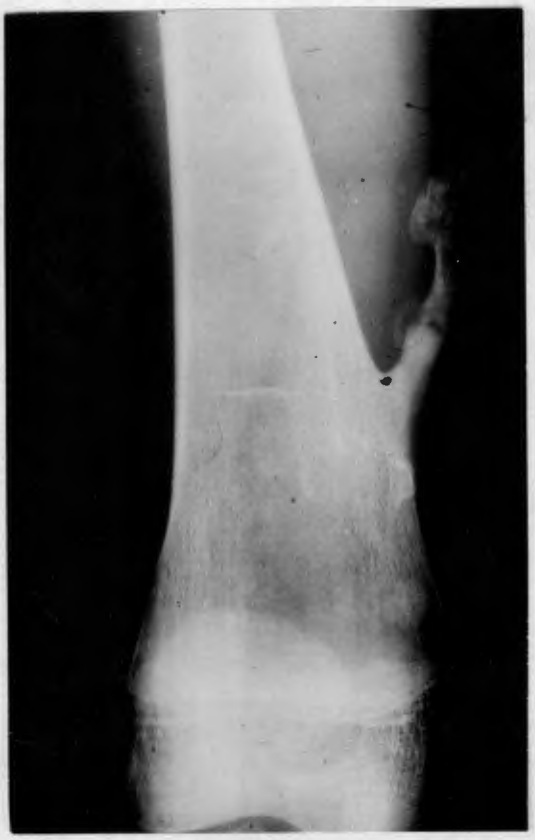


FIG. 24

Radiograph showing a fracture of a stalked exostosis.

Fracture of an Exostosis.

Fracture of a stalked exostosis excites the clinician's curiosity but causes little concern to the patient. It occurred in two cases of the present series(Fig. 24).

Exostosis Bursata.

The development of a bursa over an exostosis often goes unnoticed; a careful search of the affected areas will reveal at least one bursa in almost every case. Only three of the index patients, however, sought medical advice for this complication.

At operation the bursal sac may be found to enclose the exostosis completely, being attached at its base, and filled with mucinous fluid. In one such case the bursa contained innumerable "rice bodies", which were thought to have formed from the lining of the sac. Radio-opaque, osteocartilaginous loose bodies have been encountered as well, though not in the present series (100).

Chondrosarcoma.

The most serious complication of all is malignant change in one or other of the cartilage-capped exostoses. This subject is sufficiently important to warrant separate discussion.

Apart from the patient who died due to urinary obstruction and renal failure, there were three other deaths among the 56 index patients. None of these were attributable to the bone disease. One patient had a primary carcinoma of the lung, another died of cardiac failure, and the third of bronchopneumonia.

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CHAPTER X.

TREATMENT.

In the absence of complications, pain is the commonest indication for surgical removal of an exostosis. The cosmetic appearance sometimes warrants surgical treatment as well.

However, there can be no question of trying to remove large numbers of exostoses in an attempt to improve the appearance or forestall the development of chondrosarcoma. Even the removal of solitary lesions is attended by complications in a disturbing proportion of cases. The operative complications in the patients treated at the Royal National Orthopaedic Hospital are shown in Table IV.

TABLE IV

POST-OPERATIVE COMPLICATIONS IN PATIENTS WITH MULTIPLE EXOSTOSIS

Number of Cases operated on:		**45**
Post-operative Complications:		**9**
Nerve lesions (permanent):	**3**	
Nerve lesions (temporary):	**2**	
Limitation of Joint movement:	**2**	
Continued pain:	**1**	
Keloid:	**1**	

Towards the end of the growth period, and certainly throughout adult life, the patient should return at regular intervals of six months or a year for interview and examination. Any lump that appears to be increasing in size, however slowly and unobtrusively, should be removed forthwith! At this stage persistent growth, or renewed growth, may be the only sign of malignant change, preceding the recognisable histological features of chondrosarcoma by several years.

Large, calcified exostoses, such as the one in Fig. 16, do not necessarily call for removal if they are obviously benign. However, in certain sites, especially the pelvis, their continued growth may go unnoticed by the patient for many years. For this reason alone they constitute a greater danger than exostoses in more conspicuous places. Their progress should be followed radiologically; here again, any enlargement, regardless of the benign character of the calcification, should lead to removal of the exostosis.

The patient with deformity of the forearm and wrist, due to bowing of radius, will frequently seek medical advice and may even request surgical correction for purely cosmetic reasons. As the basic defect here lies in the ulna, and the radial deformity is a secondary phenomenon (see Chapter XVI), there is little that can be

done to counteract its development. It is noteworthy, however, that radial bowing never occurs if the radio-humeral joint dislocates (Fig.52). Working on this knowledge, the author has, in one case, excised the proximal end of the radius in a child's forearm where the deformity was already present at the age of six and increasing steadily. No further bowing occurred over the next two years. The unpredictable effects of this operation on elbow function makes it unwise to apply this treatment to any but the severe and progressive type of forearm deformity.

Pes valgus seldom needs more than postural treatment with corrective insoles. Genu valgum, on the other hand, may be severe enough to require tibial or femoral osteotomy at the end of the growth period (Fig.13,b). This was necessary in two of the 56 index patients in this series.

Surgical technique.

The surgical removal of an offending exostosis is seldom a difficult procedure. Reason, and the exhortations of pathologists, dictate that the exostosis be removed intact, with the piece of normal cortex from which it arises, leaving no remnant of the cartilage cap behind. Judging by the specimens examined, this rule is often broken, with the line of excision running through apparently active cartilage. Four patients in whom cartilaginous tissue was

presumed to have been left behind were examined with particular care. In three there was no sign whatever of a recurrence of the exostosis. In the fourth, the shreds of tissue which were visible radiologically soon after operation, proceeded to grow independently of the parent bone in the shape of a ball, until removed two years later (see Fig.46).

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CHAPTER XI.

CHONDROSARCOMA.

The occurrence of chondrosarcoma in hereditary multiple exostosis has been recognised from the earliest times. Indeed, the first recorded case history of hereditary multiple exostosis in the medical literature was that of a young mother of 30 years with numerous "bony tubercles" on the ribs, tibiae, femora and elsewhere, who later developed a chondrosarcoma at the distal end of the right femur (Boyer, 1914) (17). The exostosis here, which had been present for many years, suddenly started to enlarge after her fifth pregnancy. As the swelling could not be reduced by conservative measures the limb was amputated two months later. From Boyer's description it seems clear that this was a malignant tumour. We learn that it was large and lobulated, mainly cartilaginous but bony at its base. The other bones in the amputated limb were studded with typical benign, cartilage-capped exostoses.

The difficulties of diagnosis and treatment are seldom resolved as speedily as in Boyer's case. The dividing line between "abnormal growth" and "neoplasia" in a cartilage-capped exostosis is hard to determine. An increase in size after the normal period of growth might suggest the possibility of malignant change; but children,

too, suffer this complication (Bennett & Berkheimer, 1941) (11) and here the point of departure from benign growth is imperceptible. Moreover, the histological diagnosis of chondrosarcoma is notoriously difficult and even an experienced pathologist would be forgiven for expressing an honest doubt about a diagnosis which could well lead to a hindquarter or a forequarter amputation!

Notwithstanding the high incidence of chondrosarcoma in multiple exostosis reported from some clinics (30; 77) the number of cases reliably described in the literature is comparatively small. In some of the earlier reports the diagnosis, either of the primary condition or the superimposed sarcoma, is extremely doubtful (98). In others the subject is confused by ambiguous references such as "chondroma developing in an exostosis" or "recurrent chondroma."

Twenty-three reliably documented cases (including that of Boyer (17) have been extracted from the European and American literature (Table V).

TABLE V

CHONDROSARCOMA IN HEREDITARY MULTIPLE EXOSTOSIS
CASE REPORTS IN THE MEDICAL LITERATURE.

AUTHOR		Number of cases	Site of sarcoma
Boyer	(1814)	1	Distal femur
Weber	(1866)	1	Pelvis
Barlow	(1895)	1	Distal femur
Phemister	(1930)	2	Proximal tibia Distal femur
Belot & Simchowitz	(1936)	1	Proximal humerus
Gardner	(1937)	2	Pelvis Proximal femur
Fennel	(1938)	1	Distal femur
Bennett & Berkheimer	(1941)	1	Distal femur
Jaffe	(1943)	3	- - - - - - - - -
Geschickter & Copeland	(1949)	2	- - - - - - - - -
Drevon et al.	(1950)	1	Proximal humerus
Ellis & Taylor	(1951)	1	Proximal femur
Monro & Golding	(1951)	1	Pelvis
Flatt	(1955)	1	Proximal tibia
Gross et al.	(1957)	1	Pelvis
Knight	(1960)	3	Pelvis (2) Tibia
Unreported cases		2	Pelvis Proximal femur

The case notes, radiographs and histological sections of three of these reported cases have been studied by the author; indeed, one of Gardner's patients (1937) (54) is included in the "secondary" cases of the present series (see Pedigree No. 29, IV, 1.). Another two cases, quite outside this series and not reported elsewhere, were brought to the author's notice at the Massachusetts General Hospital, Boston. Together, these 25 cases form the background to the description that follows.

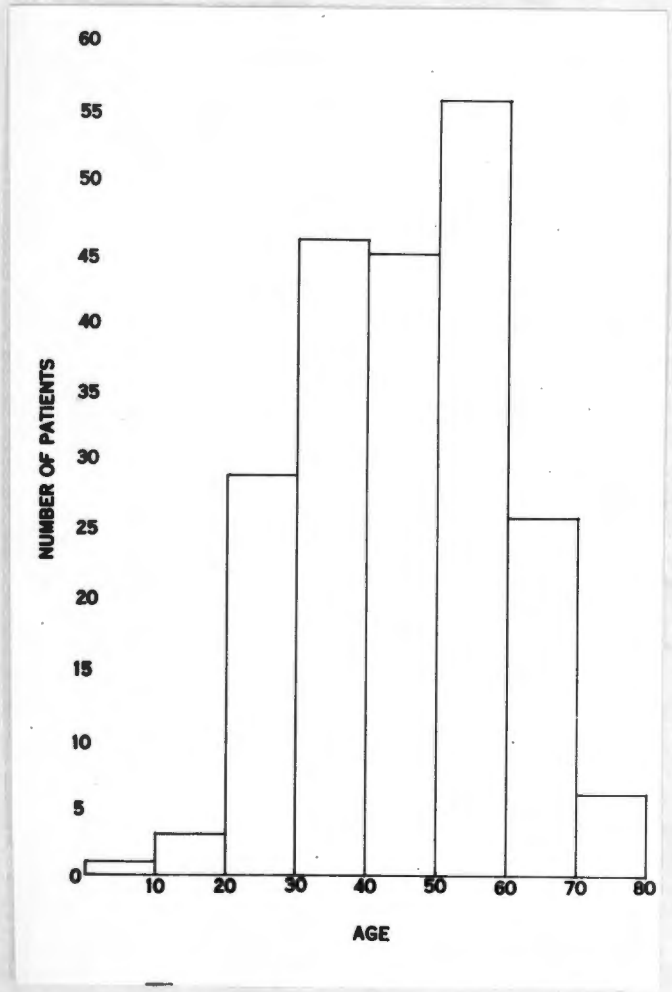
Incidence.

The incidence of malignant change in multiple exostosis is generally believed to be about five per cent (Aegerter & Kirkpatrick, 1958) (2). However, there are wide variations from this figure, depending on the age distribution of the particular series, the criteria of malignancy and the degree of specialisation in the centre from which the report emanates. Dahlin (1957) (30) on the basis of 272 cases of osteochondroma of all types studied at the Mayo Clinic, estimated the incidence of chondrosarcoma in patients with multiple exostosis at more than 10 per cent. Jaffe, in 1943 (76) reported three cases of chondrosarcoma among 28 patients with hereditary multiple exostosis, an incidence of 11 per cent. And this, he believed, was a conservative estimate because the follow-up was incomplete. "In fact," says Jaffe in 1958 (77), "a complicating chondrosarcoma can probably be expected, sooner or later, in about 25 per cent of cases of multiple exostosis."

These figures are much higher than the experience of most clinicians suggests. None of the 56 index patients in the present series developed this complication. Among the secondary cases only one example of a histologically proven chondrosarcoma was discovered (Pedigree No. 29, IV, 1.).

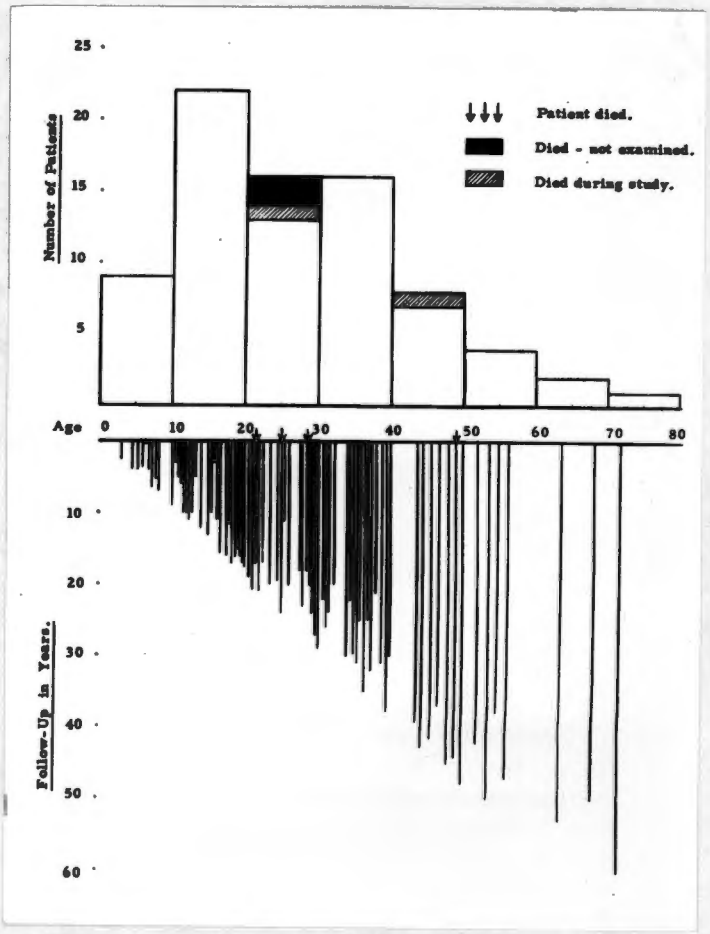
Clearly the age-distribution of the series studied is important. In a report on 212 cases of chondrosarcoma treated at the Mayo Clinic between 1905 and 1955, Dahlin and Henderson (31) found that 63 per cent presented after the fourth decade (Fig. 25, a). The age distribution of the present series at the time of examination by the author, and the period of follow-up, is shown for comparison (Fig. 25, b). Only 19 per cent had passed the fourth decade and half of them were still under the age of 25 years. It is, in fact, impossible to give a valid figure for the incidence of malignant change until all these patients have died, and even then innumerable exostoses would have been excised that might otherwise have given rise to chondrosarcomas. Equally, though, the series of Jaffe (1958) (77) and Dahlin (1957) (30) may be weighted in the opposite direction, for the latter has been prompted, elsewhere, to comment that ".....the high percentage of referred patients (at the Mayo Clinic) would tend to make the incidence of chondrosarcoma seen at the Clinic relatively high." (31).

FIG. 25



(a)

Age distribution of patients with chondrosarcoma in Dahlin and Henderson's series of 212 cases (31).



(b)

Age distribution and period of follow-up at time of examination in the present series of patients with multiple exostosis.

Familial Incidence.

It is most unusual to find this complication described in more than one member of an affected family. Knight (1960) (86) reported its occurrence in three brothers known to have multiple exostosis, but in two of them the diagnosis was based entirely on verbal evidence.

Age and Sex.

Most of the cases reported, as well as the ones described here, were diagnosed in adulthood but children are well known to suffer this complication too (11; 35). Males predominate slightly over females. Gardner (1937) (54) pointed out that when the complication occurs in females it is usually between the ages of 20 and 30 whereas the males are usually over 40.

Site.

The site of the exostosis developing a chondrosarcoma was known in 20 of the cases reviewed here (Table V). In exactly half of them it was the region around the hip, the pelvis in seven and the proximal end of the femur in three. Jaffe (77) and Dahlin and Henderson (31) have also commented on the frequency with which this area is affected by chondrosarcoma. Other sites reported in the literature were the distal end of the femur (five cases), the proximal end of the tibia (three cases), and the proximal end of the humerus (two cases).

It was noted in the present study how often the region around the hip - and the pelvis in particular - harboured exostoses of considerable size without the patient being aware of them. Indeed, wherever the lesions are inconspicuous they tend to reach a size which, in any other situation, would have called for their removal. It is possible that this, rather than any pathological peculiarity, accounts for the apparent predilection for the sites described.

Clinical Features.

Trauma, and usually severe trauma, antedated the change in the character of the lesion in many of the recorded cases. Whether this really initiates the malignant change is still doubtful but the relationship is real enough to make it obligatory to re-examine at frequent intervals every patient who reports an injury of more than minor degree.

In three of the reported cases the malignant change followed soon after a pregnancy(17; 54; 50). However, the latter event occurs sufficiently frequently to make a real causal relationship extremely doubtful.

The only clinical feature likely to emerge is a slow but definite increase in the size of one of the bony swellings after the end of the normal growth period. Often this is so gradual as to allay all suspicion and it may be eight or ten years before the patient consults

his doctor again. In the majority of cases the tumour is already of an alarming size by the time it is operated upon. There may be some discomfort from pressure on adjacent organs but the swelling itself is usually painless.

Recurrence of the tumour after an adequate excision of a "benign" exostosis should excite the suspicion of an aggressive lesion. This may occur repeatedly, with subsequent lesions showing a gradual change in histological pattern towards malignancy (77).

Radiological Features.

Only rarely is the radiograph by itself conclusive; more often it has to be carefully weighed against all the other evidence available. Patchy or streaky calcification of the cartilaginous cap is generally more widespread, of more variable density and more indefinitely confined at the peripheri of the tumour mass than that seen in a benign exostosis (compare Figs. 16, 19 and 26). Successive radiographs may show a gradual increase in the size of the tumour. This by itself is highly suspicious. When accompanied by signs of progressive invasion and destruction of bone the diagnosis of malignant change is certain (Fig. 26).

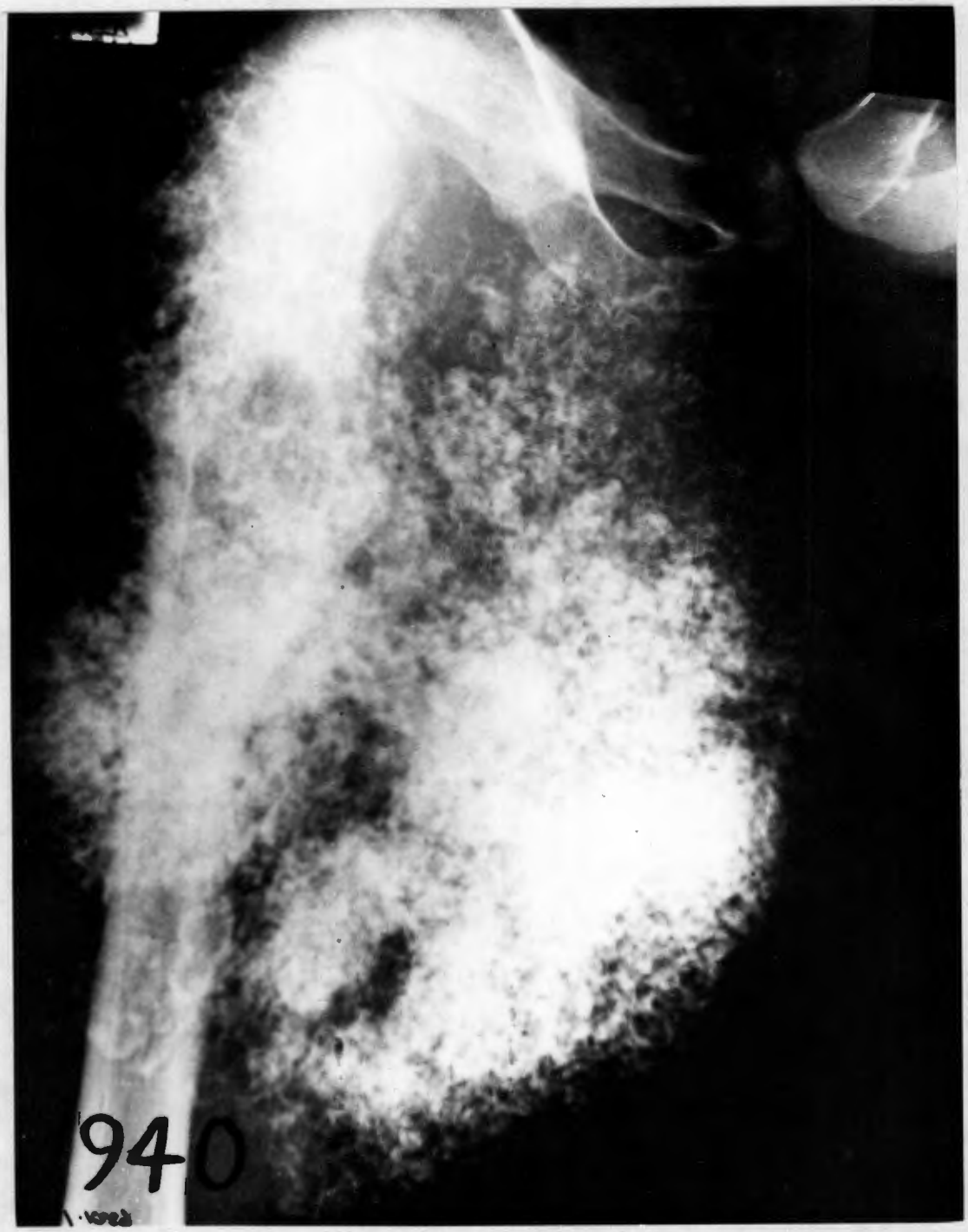


FIG. 26

RAdiograph of the proximal end of the right femur where a chondrosarcoma has developed in a cartilage-capped exostosis. The calcified cartilage shows extension into the soft tissues and there is bone destruction in several areas. The tumour had increased considerably in size over the previous two years.

Morbid Anatomy.

Although, from the presence of multiple exostoses elsewhere, there is never any doubt about the origin of the chondrosarcoma, the malignant lesion may have destroyed all signs of the exostosis in which it arose, in which case one may be confronted at operation by a large, lobulated, fleshy tumour invading the soft-tissues locally. At the other extreme, a well defined cartilaginous tumour may appear quite benign until examined microscopically.

Jaffe's and Lichtenstein's (77; 100; 101) descriptions of the histological features of chondrosarcoma have become generally accepted as the most reliable criteria of malignancy in cartilaginous tumours (31; 112). Suspicious features are :

(1) Hypercellularity of the tissue;

(2) Plumpness of the cell nuclei; and

(3) More than an occasional cell with plump double nuclei.

On these criteria alone several "borderline" lesions, and occasionally even a benign lesion, will inevitably be included in the net cast for signs of early malignant change. However, as Dahlin and Henderson (31) observe, the number of "borderline" tumours diagnosed is inversely proportionate to the experience of the pathologist. According to Jaffe, the diagnosis of chondrosarcoma is

certain if, in addition to the above features, there are :

(1) Pronounced irregularity in the size of the cells and their nuclei;

(2) Marked hyperchromatism of the nuclei;

(3) Many cells with multiple nuclei; and

(4) Large or giant cartilage cells with single or multiple nuclei. (Fig. 27).

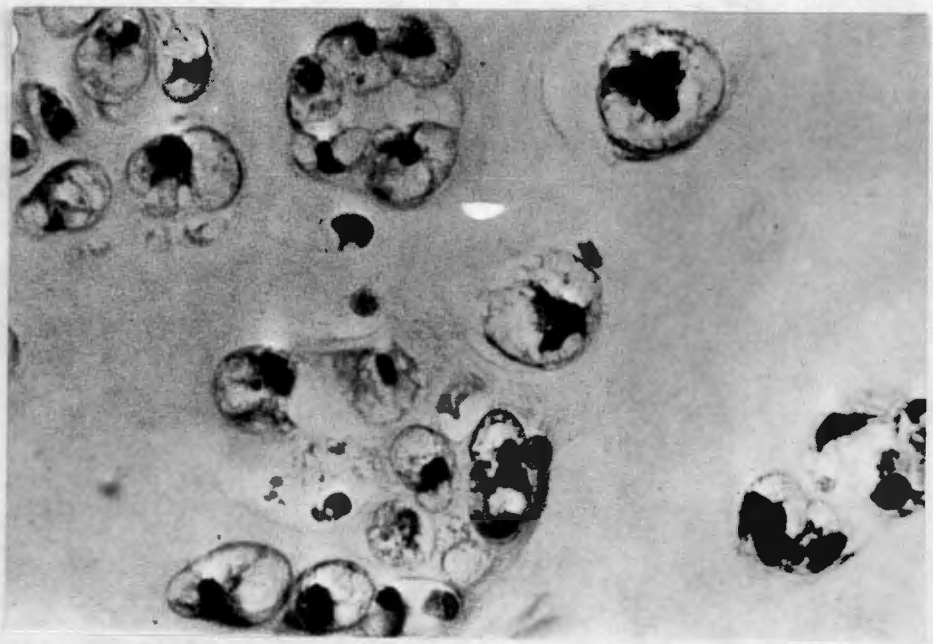


FIG. 27

Photomicrograph showing the features of a chondrosarcoma. The cells are unusually large, with plump nuclei and double nuclei. (Figure reproduced from Jaffe, 1958).

Diagnosis.

When the clinical andradiological signs point to malignancy, and the histological features described above

are present, the diagnosis of chondrosarcoma will be firm and confident. If either the clinical or the radiological signs suggest malignant change, but the histology is benign, one may be faced with one of the most taxing decisions in medicine. In these circumstances a needle biopsy cannot be relied upon; even after an incisional biopsy a negative report should not be accepted as final. The cellular appearance varies widely in different parts of the tumour and multiple blocks from different areas may have to be examined to reveal some evidence of malignancy.

Jaffe (1958) (77) has crystallised an almost unequalled experience in these words: "Altogether, in evaluating a cartilage tumour which is suspected of being a chondrosarcoma, whichever feature (pathologic or clinical) is the more sinister should be regarded as the more important." And Lichtenstein (100) somewhat less circumspect, states : "Any osteocartilaginous exostosis in an adult, and occasionally even in a younger patient, which takes on a spurt of growth, should be regarded as already a chondrosarcoma."

Although two of the reports (11; 49) listed above describe the malignant tumour as an "osteogenic sarcoma", the radiological and histological features described do not support this diagnosis unequivocally. On the available evidence it appears that the change is always to a chondrosarcoma.

Prognosis.

Although there are cases on record of secondary, peripheral chondrosarcoma proceeding to a fatal conclusion within months, the majority remain only locally malignant for several years. This is often true also of a recurrent tumour following local excision. Monro and Golding (1951) (103) reported a case of chondrosarcoma of the ilium which recurred four times after as many attempts at local excision over a period of seven years. In the end a hindquarter amputation was carried out with every hope of success; the tumour had still not metastasized. Dahlin and Henderson (31) also described a patient who had ten operations for local recurrences of a cartilaginous tumour of the iliac crest over a period of 23 years, and was still well 21 years after the last procedure!

However, these experiences are no justification for underdiagnosis or ultra-conservative treatment of the malignant tumour. The same authors (31) have stressed the need for early, adequate excision and warned of the poor long-term prognosis of most chondrosarcomata inadequately treated. Considering chondrosarcomata of all types, Dahlin and Henderson (31) found that, out of 109 patients who had received inadequate treatment, only four had remained free of recurrence for 10 years; 25 had had "massive recurrence" and no less than 80 were dead

within 10 years. Faced with these results, there is small consolation in the fact that they (and other observers) found that peripheral chondrosarcomata were less aggressive (or possibly more amenable to surgical extirpation!) than central tumours. By contrast, out of 34 patients receiving adequate, early treatment, 14 were alive and free of recurrence after 10 years.

Attempts to grade these tumours have a limited prognostic value, except that, in general, those that appear more active microscopically have a somewhat poorer prognosis (31; 112).

Treatment.

The lesson to be learnt from the cases described in the literature, as well as the three studied by the author, is that treatment must be early and adequate. Only if it is absolutely certain that a local excision will remove every shred of cartilaginous tissue, and furthermore, only if the location is such that a recurrence would still be operable, should a local resection be undertaken. Where these factors cannot be assured, an amputation is the correct treatment. Clearly, in the case of the scapula and shoulder or the pelvis and hip, this usually means a fore-or hindquarter ablation. However, Jackson Burrows (18) and Charnley (20) have successfully excised chondrosarcomas of the proximal end of the femur and replaced the bone by a large, articulating, metal prosthesis.

Radiation therapy has no effect on this tumour though it has been applied pre-operatively to reduce the possibility

of implantation in the wound(34; 81).

If a frozen section is to be examined the tissue should be taken from a viable, uncalcified part of the tumour. If there is doubt about its interpretation, definitive surgery should await examination of a fixed, paraffin section.

If the tumour is to be locally excised the biopsy wound should be removed with the lesion. The chondrosarcoma should not be incised again but should be removed en bloc with the surrounding tissues attached.

ILLUSTRATIVE CASES IN THE PRESENT SERIES.

Case 1, a 50-year old woman. For as long as she could recall she had been aware of multiple swellings around the joints and over the scapulae. At the age of 50 years, while attending hospital for some unrelated condition, a large, firm tumour over the left scapula attracted the surgeon's attention. The radiographic appearances were thought to indicate something more sinister than a benign exostosis and the patient was referred to the Royal National Orthopaedic Hospital for further assessment.

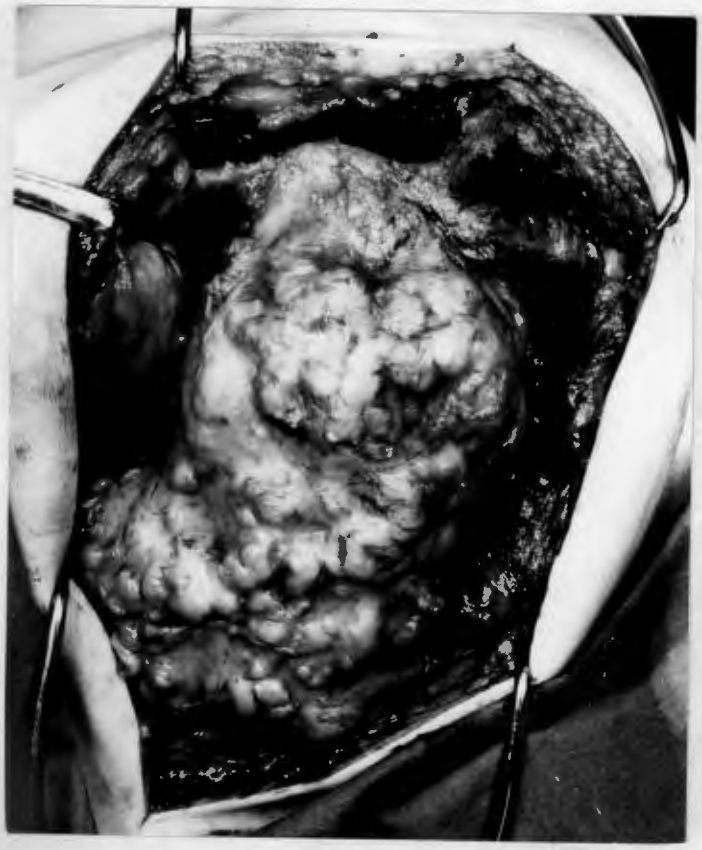
On examination she presented the characteristic features of hereditary multiple exostosis. Her son, her father and two sisters were similarly affected (Pedigree No. 36, II, 6). A large exostosis at the

FIG. 28

Large exostosis of the left scapula showing dense calcification of the cartilage cap.

(a)

(b)



(c)

(d)

vertebral border of the left scapula extended almost to the opposite scapula (Fig. 28,a). It was firm and coarsely lobulated. It had not increased in size since the end of adolescence.

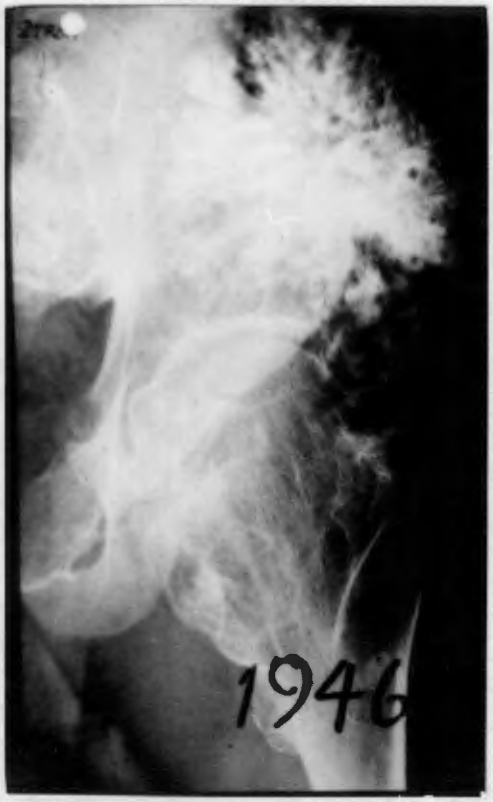
A radiograph showed a large, heavily calcified mass obscuring the left scapula (Fig.28,b). The calcification was uniformly dense and well demarcated peripherally. There was no bone destruction.

This tumour was confidently diagnosed as a benign, cartilage-capped exostosis with degeneration and calcification. A local excision was advised.

At operation, the lobulated tumour was removed with a segment of the vertebral border of the scapula (Fig.28,c). A cross section showed that the bulk of it consisted of calcified cartilage and calcium detritus extending throughout the exostosis (Fig.28,d). Seven years later she was well and there was no recurrence.

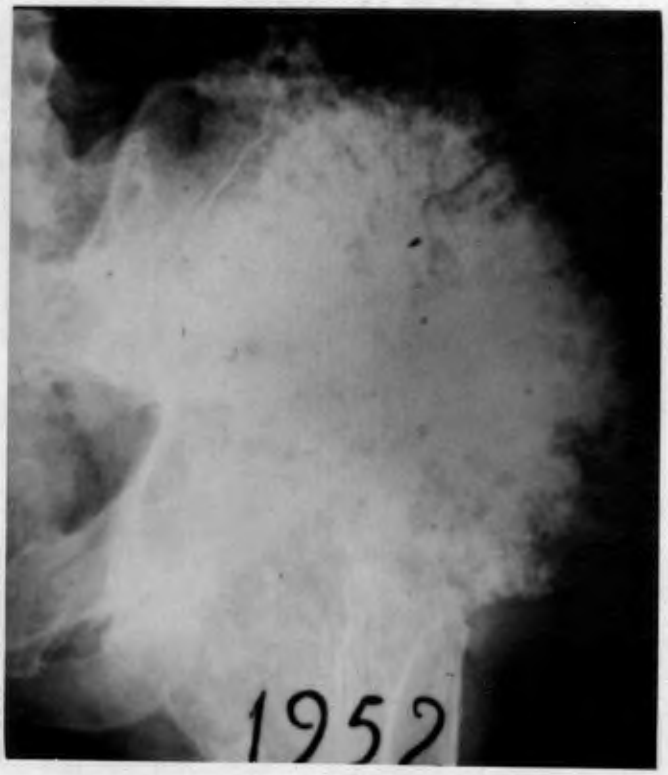
Neither the clinical nor the radiographic appearances suggested malignant change and a local excision proved to be justified.

Case 2, a 27-year old man. This patient was first seen at the age of 17 with bony swellings around the knees. A diagnosis of multiple exostosis was confirmed radiologically. One exostosis in particular, on the left iliac bone, was unusually large and the patient was advised to return at regular intervals for radiological examination (Fig.29,a). From the serial radiographs



(a)

(b)



(c)

FIG. 29

Radiographs of a large pelvic exostosis, showing the steady increase in size.

over the next 10 years it became obvious that the tumour was increasing steadily in size (Figs. 29,b and c). Although there were no other radiological features suggesting malignant change he was urged repeatedly to have the tumour excised and submitted to histological examination. This he adamantly refused to do.

At the age of 29 he was investigated elsewhere for an intractable cough. A diagnosis of bronchial carcinoma was confirmed by a biopsy and a right pneumonectomy was carried out forthwith. He became profoundly shocked after the operation and died. There was no question of the pulmonary tumour being a metastatic lesion. The diagnosis of chondrosarcoma of the ilium was never confirmed.

In spite of the fact that this tumour grew steadily larger there was no other sign of malignant transformation over a period of 12 years. Characteristically these lesions metastasize very late; indeed, the patient may die of some quite unrelated condition before the chondrosarcoma proves its malevolence.

Case 3, a young male. This was the only case of proven malignancy in the present series. He was not one of the original index patients but came to the author's notice through a sister who attended the Royal National Orthopaedic Hospital (Pedigree No. 29).

As a boy he had been aware of multiple bony swellings around the joints. His paternal grandfather,

his father and two sisters had similar lesions. At the age of 15 years he injured his right thigh in a bicycle accident. Six months later a lump appeared at the site of injury and increased considerably in size over the next two years.

Alarmed at the fact that this swelling continued to enlarge, unlike any of the other nodules, he consulted a doctor and was immediately referred to St. Bartholomew's Hospital, London.

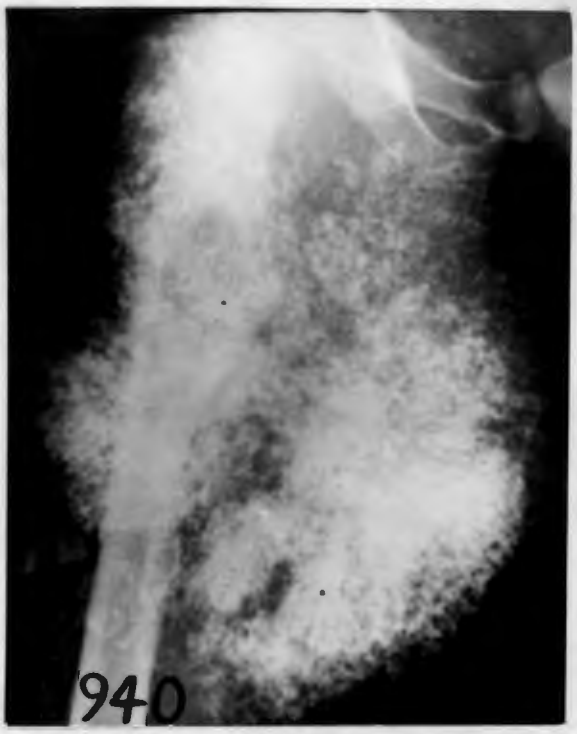
The patient was then 18 years old. He presented the characteristic features of multiple exostosis. At the proximal end of the right femur, however, there was an unusually large mass, lobular in outline, soft in some parts and bony hard in others. A radiograph showed this to be a cartilage-capped exostosis with diffuse calcification of the cartilaginous part of the tumour (Fig. 30,a). There was no certain evidence of malignancy.

A clinical diagnosis of chondrosarcoma was made; amputation was advised but refused by the patient.

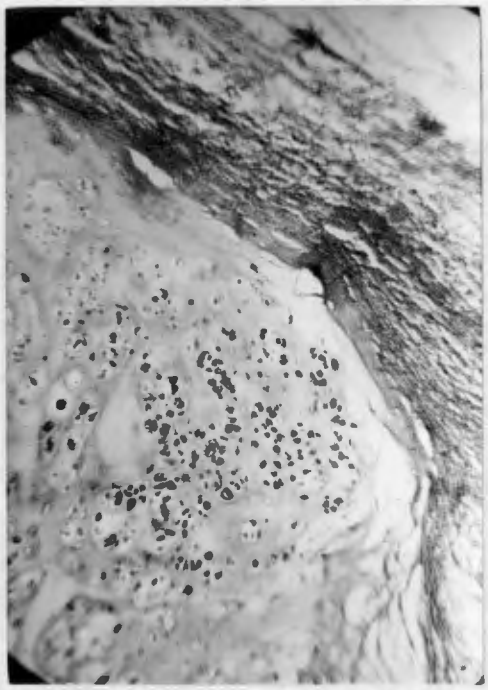
In spite of a course of radiation therapy the tumour continued to enlarge. Four years later there was radiological evidence of bone destruction and soft-tissue invasion (Fig.30,b).

At the age of 23 years he agreed to surgical treatment. There was still no evidence of metastases

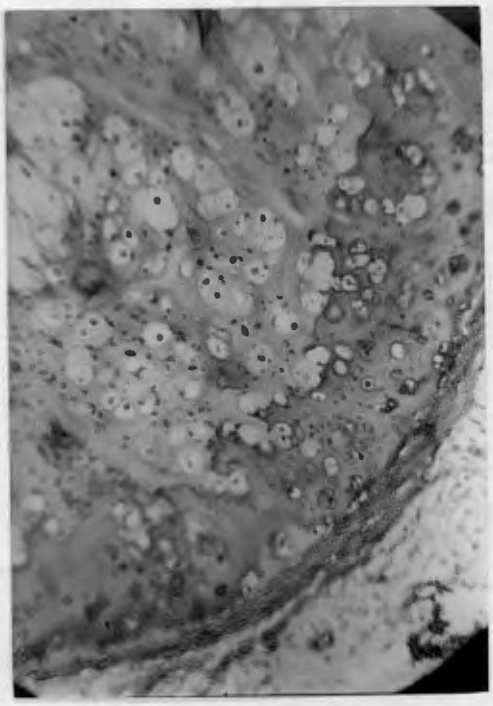
(a)



(b)



(c)



(d)

FIG. 30

(a) & (b). Serial radiographs showing the increase in size of the femoral exostosis associated, later, with bone destruction (same case as Fig. 26).

(c) & (d). Photomicrographs of tissue obtained at biopsy. Note the cellularity and pleomorphism of this tissue.

but a biopsy now showed the histological features of a chondrosarcoma (Fig.30,c & d).

A disarticulation of the hip was followed by a steady deterioration of his general condition and he died soon afterwards.

The importance of early diagnosis and treatment, or the slow but inexorably fatal progress of the untreated secondary chondrosarcoma are vividly illustrated by this unfortunate case.

In the wider context, it reminds us once again of the grave potential residing in the innocent lesions of hereditary multiple exostosis.

PART III

"ANTECEDENTS AND CONSEQUENCES"

"..... the investigations of science have proved beyond all doubt that there is no fact which exists in pure isolation, but that every experience, however objective it may seem, inevitably becomes enveloped in a complex of assumptions as soon as the scientist attempts to explain it."

Pierre Teilhard de Chardin.
THE PHENOMENON OF MAN.

INTRODUCTION.

It is tempting to say that diaphysial aclasis and all its manifestations are simply the product of a particular genetic abnormality and regard the matter as closed. This concept of hereditary disease is commonly held, even today; yet a moment's reflection will show its limitations. It is the tendency to disease (or health) which is inherited in the genotype; the manifestation itself, whether of health or disease, is a state of the phenotype and the resultant of several - possibly conflicting - tendencies, of which the genotypic abnormality is one. The type of bone affected, the manner of growth at the particular site, the ageof onset and the length of time during which the effect is active, the controlling or abetting influences of adjacent structures, all are important in determining the final appearance of multiple exostosis. The complete elucidation of its pathogenesis and ultimate form begins with the inherited, abnormal trait, extends beyond the defective gene, beyond the fundamental, embryonic error to the abnormality of bone growth and ossification. It has yet to be fully realised.

First, then, we shall consider the genetic pattern in which the disease operates. With the genotype established, we may extend the field of enquiry to the way in which the disease evolves in the phenotype and,

finally, to an elucidation of the abnormality of growth (a conjunction of order and disorder in endochondral ossification) which determines the form of the disease as it has been described in the foregoing chapters.

C H A P T E R XII.

THE HEREDITARY CHARACTERISTICS OF MULTIPLE EXOSTOSIS.

INTRODUCTION:

The occurrence of the disease in several members of the same family was noted in the first case of multiple exostosis described in the medical literature (Boyer, 1814) (17). As the disease became more generally recognised a fairly constant hereditary pattern began to appear. In 1925 Stocks and Barrington were able to collect 1,124 case histories from the medical literature to produce their classic review of the subject in the Treasury of Human Inheritance (135). In 727 of these cases, drawn from 163 families, there was a definite history of other members of the family being involved. From a simple analysis of the reported cases they came to the following conclusions :

1. Approximately two-thirds of all patients with multiple exostosis were known to have had an affected relative, usually one or other of the parents.

2. There was no instance of a father transmitting the disease without himself being affected. However, transmission of the disease through an unaffected female occurred in one-quarter of the cases inheriting the disease from the mother's side.

3. The sex ratio of all cases showed a 7:3 preponderance of males.

4. Affected fathers had a much higher incidence of affected sons among their children than affected mothers.

5. "Enchondromata may occur in some members of a family and exostoses in others, and any kind of admixture of the two disorders in families or cross-inheritance between them seems to be possible."

Since Stocks and Barrington did not examine any of the cases themselves, the accuracy of the sources upon which they drew is of the greatest importance. Unfortunately even the most reliable accounts of those times often contained examples which, by present-day criteria, would not have been regarded as hereditary multiple exostosis. These diagnostic chimera were discussed in Chapter VII. Their influence on Stocks and Barrington's work is reflected in the last of the conclusions quoted above. Enchondromatosis is now known to be a distinct and separate entity which never occurs with hereditary multiple exostosis.

Likewise, the family histories in the early reports were usually unconfirmed. There is considerable doubt about the statement that the disease can be passed to a child by an unaffected mother. Stocks and Barrington

quote 13 pedigrees showing this phenomenon; on review not one is convincingly proved, however. In Pedigrees 45, 129, 137 and 156 there is no indication whether the female subject concerned was examined or not. In Pedigrees 13, 17, 19, 127, 151 and 159 the authors admit that the subject in question was not examined.

Although Stocks and Barrington did not, themselves, undertake any formal Mendelian analysis of these cases, the pedigrees suggested that the disorder was transmitted by an autosomal dominant gene, with the female transmitter occasionally remaining unaffected. Moreover, this incomplete manifestation of the disease in the female went hand in hand with a diminished ratio of affected to unaffected females as compared with males.

This degree of incomplete manifestation was not observed by Langenskiöld in the series which he reported at about the same time (93) nor did it occur in the large family reported by Vanzant and Vanzant in 1942 (140). In this family of 78 members, there were altogether 65 siblings; the ratio of affected to unaffected males was 18:15 and of females 17:15.

Nevertheless, Stocks and Barrington's main conclusions have never been seriously questioned. The fact that males were affected more than twice as often as females has been widely accepted as one of the curious anomalies of the disease.

In 1948 Harris (69) undertook a re-analysis of Stocks and Barrington's data and came to the conclusion that, although the abnormality was always transmitted as a simple dominant, the disease was often suppressed in the female by a second, autosomal modifying gene. He proceeded to test this hypothesis against the data of Stocks and Barrington and found that he was able to predict correctly the sex ratio of the affected offspring of different groups of matings as well as the frequency of different parental pairs among the 163 families quoted.

In a genetic study of 21 patients (six families) with diaphysial aclasis Krooth, Macklin and Hilbish (1961) (87) gave special consideration to this question, but they were unable to test Harris's hypothesis as their series was too small. No further studies along these lines have been reported; the entire subject is due for a critical re-evaluation.

The present study is based on an investigation of 46 index patients (propositi) and 84 affected relatives drawn from a total of 39 families. The methods employed in collecting the data are described in Chapter III. The pedigrees of these 39 families are presented in Appendix I.

For the sake of completeness all the pedigrees are given, but numbers 11, 24, 37 and 38 are insufficiently reliable to stand analysis of the sort proposed by Harris. The findings in the remaining 35 families (42 propositi) are presented here.

RESULTS.

Sex Ratio. The sex ratio of the 42 propositi was 22 males to 20 females. Among the secondary cases who were examined there were 21 males and 20 females with multiple exostosis.

Children. There were 15 children of propositi, of whom eight were affected - four males and four females.

Parents. One parent was affected in 26 of the 42 cases, the father in 16 and the mother in 10. Those with neither parent affected might be attributed to fresh mutation. These altogether had 31 sibs, all unaffected. No case was encountered, either among the index patients or among the secondary cases, where an aunt, uncle, cousin or grandparent was affected when both parents were free of the disease.

Sibs. Among the patients with an affected parent, there were 52 sibs; 23 of these were affected and 29 were unaffected.

Grandparents. There was some evidence of a grandparent being affected in 12 of the 26 cases with an affected parent. (In three cases this information could not be obtained). Only one of these was examined and verified by the author; three were verified by another hospital or the family doctor. Five cases were reliably reported by an immediate relative; three were reported on hearsay only and these are noted as 'doubtful' in the pedigrees. There was no instance of a grandparent, but not a parent, being affected.

Children of Affected Aunts and Uncles. There were altogether 52 children of affected aunts and uncles and 162 children of unaffected aunts and uncles. Of the former group 22 children were themselves affected. Of the latter group none was found to be affected. Particular attention was paid to the children of unaffected female relatives. In three instances where typical lesions were found in the children the mother, after denying the presence of exostoses in herself, was found to be affected on radiological examination.

Intrafamilial resemblance. The type and distribution of the lesions showed no tendency to intrafamilial resemblance except in one family (Pedigree 34). In the six affected members of this family who were examined (Numbers II 1, 2 and III 2, 3, 4, 6) the lesions occurred predominantly in the hands; most of them were unaware of the presence of exostoses elsewhere until they were examined radiologically. In each case the common sites at the ends of the long bones were only mildly affected by exostoses and none of them showed the characteristic deformities associated with this disease. An uncle of the propositus (II 5) was not examined, but the author came to hear of him, by chance, in some other connection. He was evidently well known to be self-conscious about the "lumps and swellings on his hands."

DISCUSSION AND INTERPRETATION.

The results presented refer strictly to the propositi. Without going any further there are two major differences from the findings of Stocks and Barrington: firstly, the almost exact equality of the sex ratio and, secondly, the complete absence of any instance in which the disease was transmitted by an unaffected parent, male or female. The unexpected situation in which a mother denied the existence of exostoses but was found to be affected on radiological examination was encountered on three occasions and could possibly account for some of those cases reported where an unaffected mother was thought to have transmitted the disease. Krooth, Macklin and Hilbish (87) also comment on the fact that several adult females in their series had "no clinical signs of the disease", but were found to be affected on radiography. They attribute this, in part, to the greater obesity of the women, but also suggest that females may be less severely affected than males. The same observation has been made by other clinicians; the author's attention has been drawn to one such family in which "about one-fourth of the affected individuals could be diagnosed only by X-ray." (71). The possibility of a consistently milder manifestation of the disease in females has been considered, but there was no evidence, among the 76 patients examined radiologically, that females were on the whole less

severely affected than males. Nor has this fact been reported among the hundreds of papers on the subject in the medical literature. Collateral evidence for this statement is provided by the observed incidence of bony deformities in the patients studied (see Chapter XVI, Table XI). Moderate-to-severe deformities occurred in 72 per cent of males and 75 per cent of females with multiple exostosis.

The pedigrees in the present series, therefore, suggest that the disease is determined by a single gene which always produces clinical effects in the heterozygote and there is, at first sight, nothing to suggest suppression of the disease by a sex-limited modifying gene as suggested by Harris (1948) (69). There is, perhaps, a minor inconsistency in the number of affected sibs of propositi: out of 52 sibs 23 were affected and 29 were unaffected, which deviates slightly from the expected Mendelian ratio. However, the difference is not great enough to confirm reduced clinical penetrance of the gene; moreover, pedigrees 1, 3, 21 and 32 each contained at least one sib who had either died in childhood or was under three years of age when examined and might therefore have had (or later developed) minor lesions that were missed.

Given the data of Stocks and Barrington, Harris's analysis of their figures is unimpeachable

and his hypothesis provides a most acceptable explanation of their findings. It also introduces an important and original concept about the hereditary pattern of the disease. However, it is the author's belief that much of Stocks and Barrington's data was inaccurate (through no fault of their own). Apart from one or two families in the present series, such as pedigrees 18 and 22, where males were predominantly affected in successive generations, the findings presented here did not appear to be consistent with Harris's theory. A detailed analysis was therefore carried out, along the lines suggested by Harris himself, in order to test this data for agreement with his postulate.

The relative incidence of diaphysial aclasis in males and females - Harris began by assessing the "manifestation rate" of the gene for diaphysial aclasis in the two sexes; i.e. the relative incidence of the disease in males and females. Considering only sibships of seven or more individuals (which is more accurate than counting groups of two or three) he found 83 males and 77 females among Stocks and Barrington's pedigrees. Of the males, 41 were affected and 42 unaffected - the expected ratio of 1:1. Of the females, 29 were affected and 48 unaffected - a ratio of 1:1.66 - suggesting incomplete manifestation in the female. (This was also consistent with Stocks and Barrington's observation that the disease could be carried by unaffected females.)

The relative incidence of the disease in males and females of the present series is shown in Table VI (only sibships with seven or more individuals are considered).

Pedigree	Affected Males	Affected Females	Unaffected Males	Unaffected Females	Total Sibship
1 (II)	2	2	2	3	9
9 (III)	4	4	2	2	12
16 (II)	2	1	0	4	7
18 (II)	5	1	3	3	12
21 (II)	2	1	4	2	9
36 (II)	0	3	2	3	8
(III)	2	1	4	0	7
TOTALS	17	13	17	17	64

T A B L E VI.

THE RELATIVE INCIDENCE OF MULTIPLE EXOSTOSIS IN MALES AND FEMALES.

Out of 34 males, 17 were affected and 17 were unaffected, an exact 1:1 ratio, as expected. Out of 30 females, 13 were affected and 17 unaffected. The difference here is insignificant, the chisquare value being 0.47.
A cursory examination of the figures for individual sibships in this table showed that Pedigree No. 18, II contained a disproportionate number of affected males as compared with the other sibships. If this one pedigree is excluded, the manifestation rate is absolutely identical in the two sexes!

From the outset, therefore, there is a qualified disagreement with Harris's conclusions. Indeed, his basic contention that affected male parents and grandparents have a significantly higher proportion of affected males among their offspring than affected female parents and grandparents, is not borne out, either, by the pedigrees presented here - with the notable exception of Pedigree Number 18. Harris found that when the disease was inherited through the mother and grandmother approximately one-half of the affected offspring were males; when inherited through the father two-thirds of the affected children were males, and when both the father and the paternal grandfather were affected nearly three-quarters of the affected offspring were males. Excluding (for the moment) Pedigree Number 18 from the present series, the findings in the remaining 34 families are shown in

Table VII and compared with Harris's figures. (Details for each pedigree are summarised in Appendix II.) The sex ratio in the affected offspring was fairly constant for the different groups of antecedents.

ANTECEDENTS AFFECTED	SEX RATIO IN AFFECTED CHILDREN (percentage male)	
	Stocks and Barrington (163 families)	Present Series (34 families)
Father and Grandfather	71.1	41.7
Father	65.2	44.4
Mother and maternal Grandfather or Father and paternal Grandmother	65.6	57.1
Mother	57.4	42.1
Mother and Grandmother	53.3	40.0

T A B L E VII

The further contention, that the offspring of "unaffected females known to be transmitters" would also show increased evidence of the modifying gene, as expressed in a relatively high proportion of unaffected females among such offspring, could not be tested as there were no unaffected female transmitters in the present series!

The frequency of different parental pairs in the pedigrees - Harris went on to test his hypothesis in the following way. If the gene for multiple exostosis shows complete manifestation

in males and incomplete manifestation (or suppression) in females then, Harris concluded, most "unaffected father and unaffected mother" groupings in the pedigrees were actually examples of unaffected fathers and unaffected but transmitting mothers with affected offspring. It followed that the parents of affected individuals could be divided into three main groups :

(1) Affected father and unaffected mother.

(2) Unaffected father and affected mother.

(3) Unaffected father and unaffected but transmitting mother, including those pairs where this information is not certain.

Now, taking all the sibships together, it could be assumed that the abnormality would be derived in half of the affected cases from the father and in half from the mother; that is to say (assuming Harris's hypothesis to be valid) that one-half of the parental pairs should belong to Group (1) and one-half should belong to Groups (2) and (3) combined.

Considering all the sibships with two or more affected individuals, Harris found excellent agreement with the above prediction: out of 155 sibships there were 74 parental pairs of Group (1) and 73 of Groups (2) and (3) combined, conforming almost exactly to Harris's expectation (in the remaining eight instances the information was unreliable).

The same test was applied to the data obtained in the present series of cases. The results are shown in Table VIII, with Harris's figures in brackets for comparison.(Details are summarised in Appendix III.)

PARENTAL GROUPINGS ENCOUNTERED IN 30 SIBSHIPS.
(Harris's figures given in brackets)

PARENTAL GROUPINGS	FREQUENCY
Group (1): Affected father and unaffected mother	15 (74)
Group (2): Unaffected father and affected mother	10 (26)
Group (3): a) Unaffected parents but mother a known transmitter	- (10)
b) Unaffected parents, transmitter unknown	3 (37)
--------- Information unreliable	2 (8)

T A B L E VIII

It is seen that the frequency of Group (1) does indeed equal that of Groups (2) and (3) combined, but this is simply because Group (2), by itself, does not differ significantly in frequency from Group (1). There were 15 parental pairs in Group (1) and 10 in Group (2); this ratio has a chi square value of 0.30, which is below the level

of statistical significance. Certainly there is a marked deviation here from Harris's results of 74 pairs in Group (1) and 26 in Group (2)! It is perhaps even more significant that in 37 instances Harris found both the mother and the father recorded as unaffected, with no definite information as to who was the transmitter. Thus, in Stocks and Barrington's pedigrees, Group (3) is nearly twice as large as Group (2)! It seems clear to the present author, that the more detailed and reliable the examination of the patients the smaller is Group (3) likely to be.

The sex ratio of the offspring of different parental groupings - Using the same basic argument as before, and assuming that the modifying genes could be transmitted by male parents as frequently as by female parents, Harris predicted that the sex ratio of the affected offspring of affected males should be the same as the sex ratio of the affected offspring of all females together, whether overtly affected or unaffected transmitters. Thus, in terms of the parental groupings already referred to, the sex ratio of the affected children of Group (1) should be equal to the sex ratio of the affected offspring of Groups (2) and (3) combined.

On putting this to the test Harris found that Group (1) parents had 141 male and 64 female children; Groups (2) and (3) combined had 123 male and 68 female children. There is no significant difference between the ratios.

It is plain that this grouping depends largely on the"manifestation rate" of the disease in the two sexes. The relative incidence of diaphysial aclasis in males and females was discussed above and the findings in the present series were shown in Table VI. There was only one family here (Pedigree No. 18) with an obvious and marked preponderance of males, both in overall numbers and in the lines of inheritance. With this family excluded the manifestation rate was identical in the two sexes. Considering this, and the fact that there were no unaffected transmitting females in the series, it is to be expected that the sex ratios among the offspring of the different parental groupings would be consistent and in the region of 1:1. Table IX shows that this is the case (Pedigree No. 18 is excluded; the details for the others are summarised in Appendix IV).

Once again there is disagreement with Harris's conclusions qualified, as before, by the exclusion of Pedigree No. 18. This family is discussed below. The remaining 34 pedigrees lend no support to Harris's hypothesis of the existence of a sex limiting, modifying gene in diaphysial aclasis.

SEX RATIO OF OFFSPRING OF DIFFERENT PARENTAL GROUPS

(29 sibships)

PARENTAL GROUPS	Affected offspring	
	Male	Female
Group (1) : Affected father and unaffected mother	18	17
Group (2) : Unaffected father and affected mother	11	14
Group (3) : a) Unaffected parents but mother a known transmitter	0	0
b) Unaffected parents, transmitter unknown	4	3

T A B L E IX.

Pedigree No. 18 - This is a family of 51 members, charted over four generations. Of the 28 males in the family, 15 were affected by multiple exostosis and 13 were unaffected - the expected ratio of 1:1. Of the 23 females, however, only 3 were affected. This pattern was quite out of keeping with the rest of the pedigrees, but apparently conformed well with Harris's suggestion of a

modifying gene suppressing the disease in the female. The lines of inheritance were also predominantly through males.

The possibility that some cases were missed should be considered. In the third generation there were 25 cousins of the propositus; 16 of them were unaffected and 11 of these were females. None was examined by the author personally. Information about the family was obtained from the propositus, his father and an aunt (II,11). One uncle of the proband (II,1) had emigrated to America where he died three months before this study was completed. Both he and his eldest son were known to be severely affected. It was believed that he had other children as well but there was no certainty about this. An aunt (II,4) was known "with certainty" to be unaffected; her four male children (III, 5-8) have retained close contact with the propositus, who is certain they are unaffected. The information about the family of II,5 is much less definite. This uncle emigrated to Australia "before the First World War." He and his three daughters are thought to be unaffected but this cannot be relied upon completely. The family of II,8 has also lost touch with the other relatives. However, he and his eldest daughter were well known to be affected. The youngest child (III,17) had had "an operation on the fingers"; with this information it was possible to trace his hospital record and ascertain that he, too, had multiple exostosis. About the other three daughters (III,14-16) there is no reliable information.

It is seen, therefore, that there is some uncertainty about at least six of the unaffected female cousins of the propositus. In these circumstances it is difficult to state with assurance whether even this family manifests the effect described by Harris.

C O N C L U S I O N.

In the series of patients with multiple exostosis studied here, 61.9 per cent were found to have inherited the abnormality. In the remainder the disease could be attributed to fresh mutation. There is good evidence for this in families such as Pedigree No. 20, where the mother, the father and both sibs of the propositus were examined by the author and found to be unaffected. The possibility that such cases which appear in isolation might represent a different condition or phenocopies has been considered. The situation where a parent and child alone are affected, with both grandparents free, would be good evidence against this. This occurred in several pedigrees, notably numbers 5, 19 and 31, all of which are reliable.

An analysis of the data presented here shows that, in the majority of cases the disease is transmitted directly by an autosomal dominant gene which always produces clinical effects in the heterozygote. There was complete manifestation in males and females alike with no skipping of generations; about one-half of the children of affected

parents were found to have multiple exostosis; males and females were affected with equal frequency. There were no consanguineous marriages of affected individuals, but Vanzant and Vanzant have reported this situation in one family; all seven children of this union had multiple exostosis.

In these cases there is obviously no need to postulate the existence of a sex-limiting modifying gene, which was suggested by Harris (69) to explain the unusual sex distribution and genetic lineage of Stocks and Barrington's pedigrees (135).

However, one family of 51 members was encountered, in which there is at least a suggestion of some sex-limiting factor, so that Harris's hypothesis cannot yet be rejected with absolute confidence in every case.

The possibility of more than one mutant gene causing the disease cannot either be excluded with complete certainty. Pedigree No. 34 has already been referred to as showing a strong intra-familial resemblance in the form and distribution of the disease. In every affected member of this family the lesions occurred predominantly in the hands and fingers with only a few exostoses in the long bones elsewhere. In no other subject examined did the abnormality take this particular form. Neither Stocks and Barrington, nor Krooth, Macklin and Hilbish in their series found any correlation between members of the same family for the form or distribution of the disease. The family described here (No. 34) is therefore of unusual interest.

C H A P T E R XIII.

NORMAL BONE GROWTH.

"A clear appreciation of the differences between the various mechanisms of growth of bones is imperative for an understanding of the different reactions in different parts of the skeleton under pathological conditions - responses which at first seem to be haphazard."

Thus Weinman and Sicher in their book on "Bone and Bones." (151). No apology is made for pausing here to consider, in some detail, the processes of bone growth and organisation. Indeed, this knowledge is essential to a rational understanding of a developmental abnormality such as diaphysial aclasis and an appreciation of the arguments which will be used in formulating a concept of its pathogenesis in subsequent chapters.

The detailed biochemistry and biophysics of ossification will not be dealt with at all. "Osteogenesis" will be described only as it relates to the larger process of "bone growth": the former refers to the formation of bone as a tissue, the latter refers to the growth of the bone as an organ. Osteogenesis, wherever it occurs, is always the same. It involves the transformation of the local connective tissue matrix to osteoid, which then becomes impregnated with bone salts in the form of hydroxy-appatite. When this occurs in the connective

tissue adjacent to existing bone such as in the subperiosteal region, or in the primitive mesenchyme directly, we refer to it as membrane bone formation. When it is preceded by proliferation and degeneration of cartilage we refer to it as endochondral bone formation. Either of these processes may contribute to bone growth.

"Membrane" and "Cartilage" Bone.

The terms "membrane bone" and "endochondral bone" relate not so much to the formed tissue as to the pre-osseous tissue in which the bone is formed. The process of ossification, whether "in membrane" or "in cartilage" is essentially the same; the tissue which is formed thereby is structurally identical and consists,in its mature form, of lamellar bone - the characteristic tissue of the mammalian skeleton. Tiny remnants of cartilage may persist in bone formed "in cartilage", especially near the epiphysial plates, but the osseous tissue itself is indistinguishable from bone laid down "in membrane."

What is different, and of fundamental significance in a disease such as multiple exostosis which is strictly limited to endochondral bone, is the pre-osseous tissue in which the particular bone is formed. "Membrane bones" arise directly in pre-existing condensations of the embryonic mesenchyme; "cartilage bones" arise in an intermediate, cartilaginous model which, itself, has differentiated within the embryonic mesenchyme. The two processes (as they refer to the formation of bone tissue)

usually go hand-in-hand in the development of the "bone" as an organ. That is to say, most "cartilage bones" such as the long bones of the appendicular skeleton, consist, to a large extent, of membrane bone, because the subperiosteal bone, which constitutes the bulk of the diaphysial cortex, is formed in membrane. During the period of bone growth these tubular bones elongate by a process of cartilaginous growth and endochondral ossification at the epiphysial plates. This process is both preceded and followed by subperiosteal new bone formation along the diaphysis - a process of ossification "in membrane." Some of the so-called membrane bones, on the other hand, undergo transformation to cartilage immediately before ossification. This applies to the sternal and acromial ends of the clavicle.

Though closely co-ordinated during growth, there is a point of final distinction between these two processes: endochondral ossification ceases at the end of the growth period for any particular bone; membranous ossification continues to the end of life and is the basic process whereby mature bone is constantly remodelled and reconstituted.

If, therefore, it is said that the cartilage-capped exostoses arise only in bone preformed in cartilage, this statement should exclude not only the more obvious examples of membrane bone such as the vault of the skull, or the mandible, but also those elements of the "cartilage bones" that develop in membrane. The point that is being stressed is that the exostoses, which were earlier described as

being in continuity with the diaphysial cortex, nevertheless should not be expected to originate from cortical bone, which is membrane bone derived from the periosteum.

ENDOCHONDRAL OSSIFICATION AND GROWTH.

Bone growth has occupied the attention of physiologists for several centuries. (65). Lacroix (1951), Ham (1952;1957), and Weinman and Sicher (1952) have given detailed and masterly accounts of this subject.

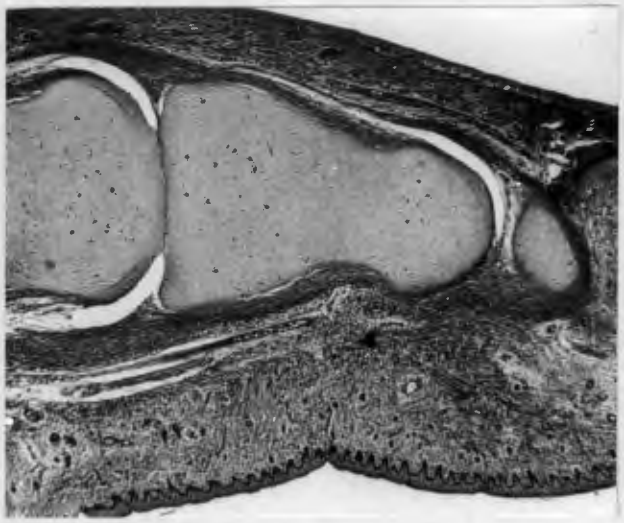
The early stages of endochondral ossification and growth are readily seen in the human foetus, and with the help of these guides the author has been able to observe and trace this process from the prenatal period to the end of growth. Details relating to the growth of the epiphysial plate and the microscopic structure of the peripheral regions of the cartilaginous disc have been gained from a study of normal tissue derived from the distal end of the femur in young people who had died in accidents (see Chapter III, Material and Methods).

The earliest stage in endochondral ossification in the embryo is a condensation of the embryonic mesenchyme at the site of the future bone. Within this area the intercellular ground substance is gradually transformed to that of cartilage and the mesenchymal cells differentiate into chondroblasts. This process extends throughout the primitive blastema until it is entirely converted into the cartilage model resembling the future bone. The

most peripheral cells are arranged into a membrane delineating the cartilage model, a primitive perichondrium with an outer, fibroblastic layer and an inner proliferative layer of mesenchymal cells, which is believed to retain its chondrogenic properties during the period of growth (67). This stage is reached before the seventh week of intra-uterine life; ossification commences soon after, when the foetus has attained a length of 25-30 mm.

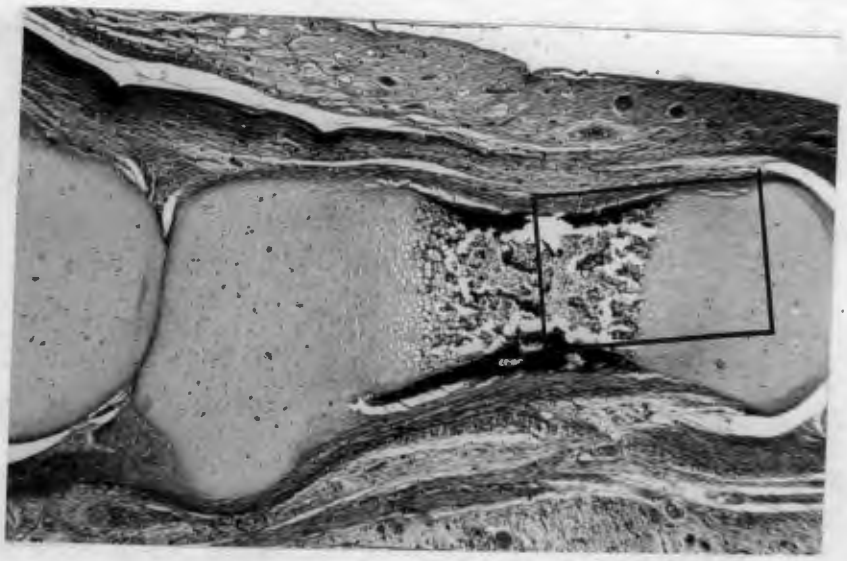
Growth of the cartilage model - The cartilage model is believed to increase its size chiefly by interstitial growth. Certainly there is an orientation of cells in the direction corresponding to the axis of elongation in the case of a tubular bone, though the author has been unable to see an axial alignment of this sort in the case of cuboidal and irregular bones such as those of the carpus. In all cases the cells at the centre of the model, be it tubular or cuboidal, undergo vacuolation and degeneration prior to ossification. In the case of a tubular bone this corresponds to its narrowest part or waist. At the ends, however, it continues to elongate and here the immature chondroblasts are arranged in stages of increasing maturity with the most immature cells at the most advanced edge of the model (Fig.31,a). There is a gradual increase in the width of the model as well and most authorities believe that this occurs, at least in part, by appositional growth from the newly formed perichondrium. (53; 67; 90; 151).

FIG. 31



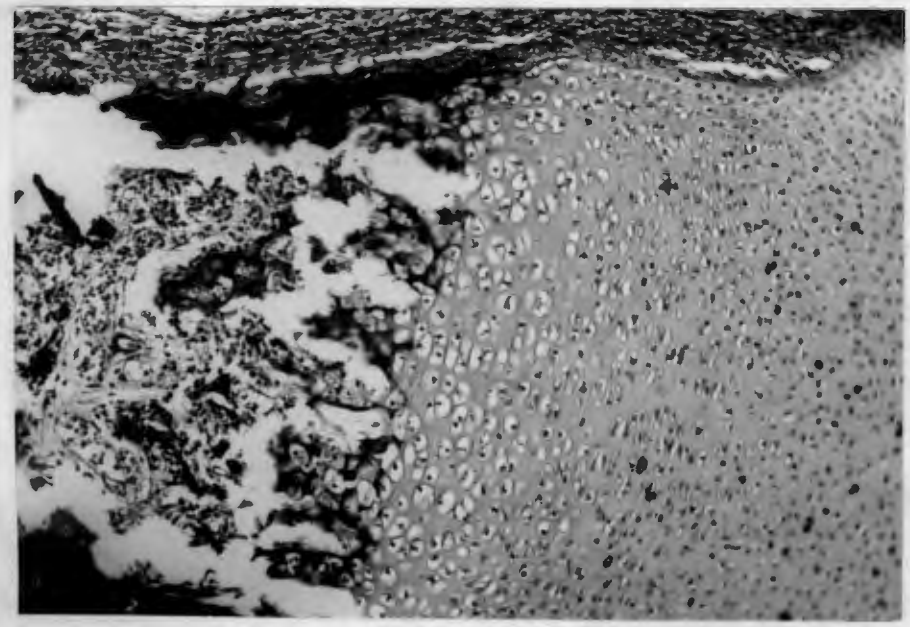
(a)

(a) Early stage in the development of a 'cartilage bone'. Ossification has not yet commenced in the cartilaginous model but the cells at the waist are less immature and less densely packed than those at the ends. (Sixth week of intrauterine life).



(b)

(b) Ossification commencing in a tubular bone. Note the periosteal cuff of bone extending proximally and distally beyond the central area of degeneration and ossification.



(c)

(c) Higher magnification of the area marked out in (b), showing the alignment of the cartilage cells, increasingly mature towards the area of ossification.

Photomicrographs prepared from human foetal material.

Further growth and ossification depends on the form of the bone to be evolved; there are important differences between the tubular bones and the irregular or cuboidal bones, while the clavicle differs from both. These will be considered separately.

THE GROWTH OF THE TUBULAR BONES

At the waist of the cartilaginous model, where the cells are the most mature, a thin sliver of calcification appears in the subperichondrial layer. Its appearance marks a change in the character of the perichondrium, possibly the result of vascularisation of the membrane. The deeper, cellular layer differentiates into osteoblasts and the membrane is now a true periosteum. New bone is deposited in the subperiosteal layer by intramembranous ossification and soon extends around the waist of the cartilage model in the form of a sheath or collar.

By this time the central part of the model is disintegrating, with calcification of the cartilaginous strands. New capillaries and osteogenic cells, derived from the periosteal sheath, grow into the central area, surrounding and invading the remnants of calcified cartilage. Wherever this vascular tissue comes in contact with degenerating cartilage ossification follows (Fig.31,b).

Interstitial growth of the cartilage model continues, with the chondroblasts orientated longitudinally, increasingly mature towards the central, newly ossified core of the model (Fig.31,c). The osteoblasts and proliferating vascular tissue are, in turn, orientated

along the same lines, around the degenerating columns of calcified cartilage, pencilling in the faint, hyaline outlines with bone.

Periosteal ossification also extends longitudinally, the advancing edges of the sheath always extending slightly ahead of the central, endochondral ossification. Havers, in 1691, stated most picturesquely that the periosteum "serves by Natures Elegance and Providence for decency in covering bone." (70). Although this term was not applied to bone development it is particularly apt in this regard, for it describes so well the ensheathing membrane, extending its protective splintage along the developing cartilage model, decently enclosing the disintegration going on within (Fig.32).

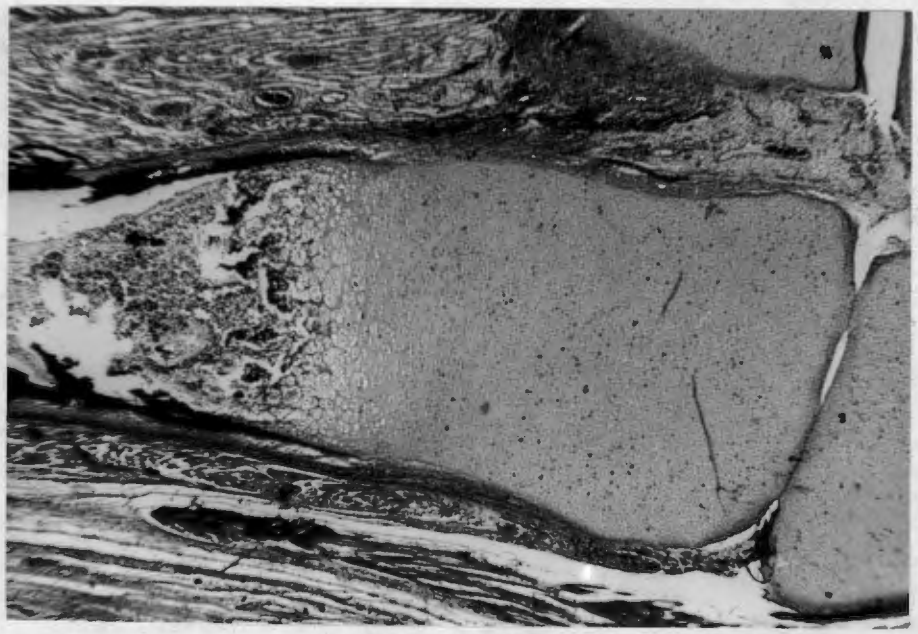


FIG. 32

Photomicrograph of a longitudinal section through part of the human phalanx (tenth week of intra - uterine life). Sub-periosteal membrane bone en- sheaths the area of degeneration and ossification.

As endochondral ossification extends towards the ends of the model the more central trabeculae are resorbed to leave a small marrow cavity. The cortex around this cavity continues to increase its dimensions by subperiosteal, appositional growth. At the very ends of the model secondary centres of ossification may now appear in the areas destined to become the epiphyses. Central ossification of the shaft slows down and the cartilage columns come to be arranged in a more orderly fashion. A recognisable disc or plate is thus defined between the diaphysial and epiphysial bone and here growth and ossification continue as before up to the end of adolescence.(Fig.33).

Further Elongation and Modelling - All further growth in the length of the tubular bone occurs at the epiphysial disc, while the increase in width is by subperiosteal appositional growth. This has been known since the early eighteenth century and the experimental work of Stephen Hales (1727), John Belchier, Duhammel (1742) and John Hunter (1764) with various types of bone marker is firmly established in the history of medicine (Keith, 1919). (82). In recent times the entire subject has been carefully explored by Lacroix (90), Ham (67) and Leblond and his colleagues (94; 95).

Endochondral ossification at the epiphysial plate proceeds by a well ordered series of stages from the proliferation of the most immature cartilage cells at the epiphysial end of the plate, through stages of increasing

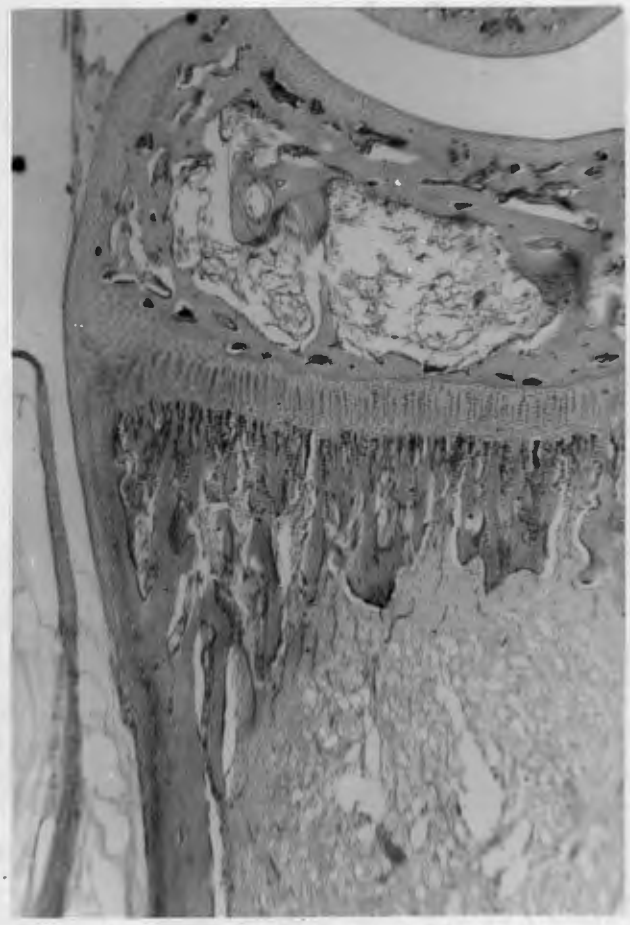
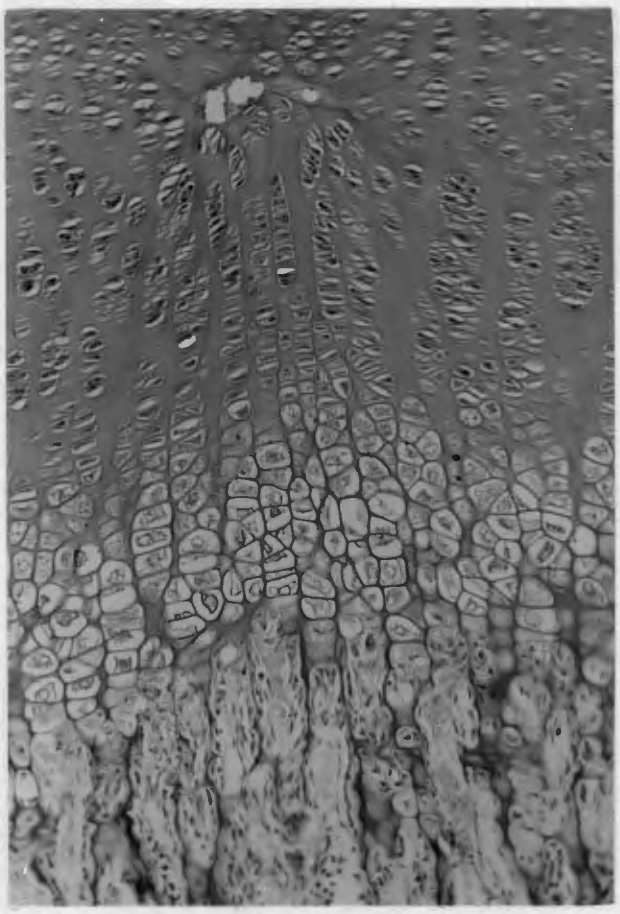


FIG. 33

Photomicrograph of a longitudinal section through the proximal end of the human tibia (foetal). The development of the epiphysial centre of ossification has defined the epiphysial plate clearly. Here the cartilage cells are arranged in regular columns and give rise to the delicate bony trabeculae of the metaphysis. (x20).

The high-power photomicrograph below shows the ordered arrangement of the cartilage cells of the epiphysial plate. Successive stages of maturation are represented by four fairly distinct zones. (x240).



...Resting zone.

...Proliferative zone.

...Zone of hypertrophic, mature cells.

...Zone of calcification.

maturation, degeneration and calcification to the final vascularisation and ossification of the cartilage columns that extend towards the diaphysis (Fig. 33). Thus, by the continuous advance of the proliferating cells in the epiphysial plate, and the simultaneous replacement of its deepest layers by bony trabeculae, the growing end of the bone is transported further and further away from the centre of the diaphysis.

That this transport of the fluted and irregularly shaped bone end can only be effected by the simultaneous processes of new-bone formation and resorption is self-evident. Figure 34 shows two tracings of the proximal end of the rat tibia taken at an interval of some weeks and superimposed upon each other. Clearly the shaded region must have been removed by osteoclastic resorption during this time. Lacroix (1951) (90) has presented convincing histological evidence of this process. A section at level (a) in any growing bone shows subperiosteal osteoclastic proliferation with numerous Howship's lacunae scolloping the periosteal surface of the cortex in the fluted part of the bone. Indeed, the narrowing part of the funnel adjacent to this may have lost its periosteal bone entirely due to osteoclastic resorption and a section taken at (b) would show the cortex here made up entirely of endochondral bone. This same effect is clearly demonstrated in the microradiograph in Figure 37. A section taken at the level (c) shows that the endosteal surface is now being resorbed

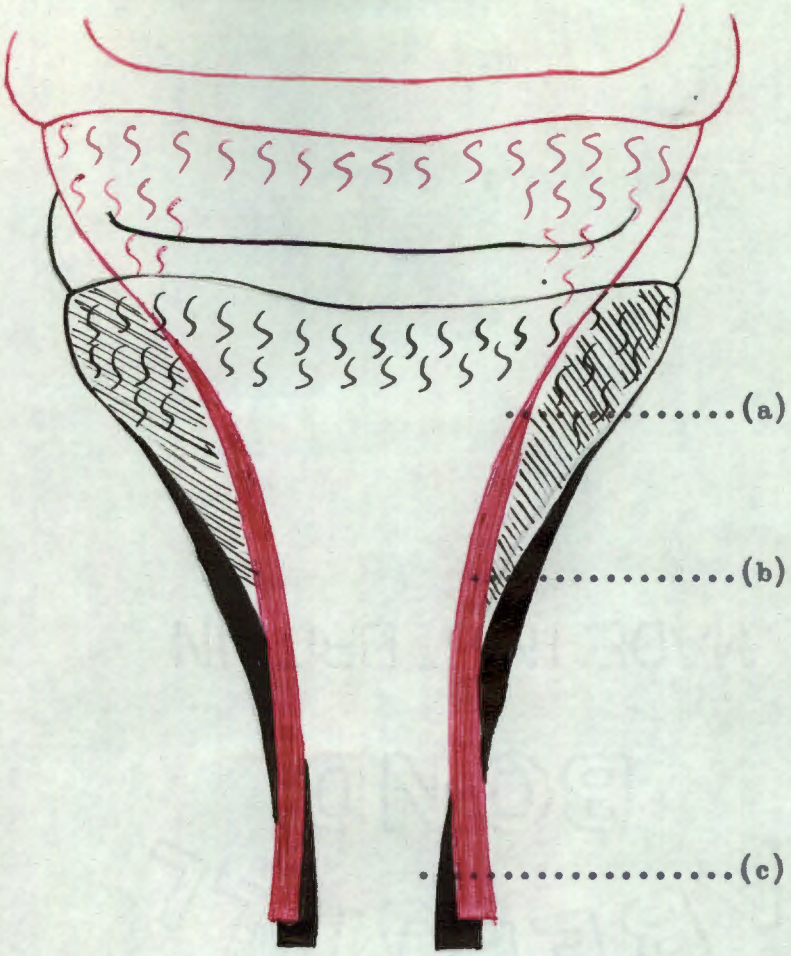


FIG. 34

Superimposed tracings of the proximal end of the rat tibia taken over an interval of several weeks. With elongation the shaded area is removed by osteoclastic resorption (level a.). At (b) the cortex consists almost entirely of endochondral bone. At (c) resorption is seen on the endosteal surface while subperiosteal newbone is added to increase the width of the diaphysis.
(After Leblond et al.)

and the bone tube is being increased in width by periosteal new bone formation (appositional growth).

Autoradiographic studies by Leblond and his colleagues (94; 95) have shown the same effect in a more vital way. By labelling the new-formed bone with P^{32} they were able to demonstrate clearly the surfaces on which radiophosphorus was deposited over a period of weeks as well

as the gradual disappearance of the labelled trabeculae at the widest part of the funnel.

This closely co-ordinated pattern of longitudinal growth and modelling is observed at all the growing ends of bone; the harmony of growth and resorption is even further extended when the bone is considered as a whole. In the humerus, for example, the proximal end, which is the more actively growing end, is modelled extensively, while the distal end, which grows much less and is, at the same time, architecturally much more complicated, shows much less evidence of osteoclastic modelling. The same applies to the slowly growing, complicated, proximal end of the ulna as compared with its distal end. These differences are extremely important and will be referred to again when the distribution of the exostoses and their relationship to the actively growing ends of bones is discussed.

Thought of in purely pictorial terms, Figure 34 suggests that a failure of modelling would result in the persistence of the shaded area. A popular theory of the pathogenesis of multiple exostosis has been built around this concept and will be referred to in a later chapter.

Organisation of the Epiphysial Disc - The organisation and orientation of the epiphysial disc are much taken for granted, yet these processes, and especially the mechanism of transverse growth of the epiphysial plate, are still

incompletely understood.

Policard (99) believed that growth and maturation of the epiphysial cartilage was secondary to metaphysial extension and a vast body of experimental work was required to refute this theory. He also suggested that the epiphysial disc is confined at its periphery in a rigid bony sheath which serves to direct the new-bone formation in the longitudinal axis of the bone. A similar belief was expressed a few years earlier by Keith (1920) (83) when he described diaphysial aclasis and suggested that the absence of this controlling sheath was responsible for the disordered transverse growth of the cartilaginous plate. The acceptance, or otherwise, of these theories must be based on the results of experiment and objective observation.

The experiments of Lacroix (1951) on the transplantation of epiphysial cartilage have shown that the growth and maturation of this tissue is the generating principle in endochondral ossification. Blocks of epiphysial cartilage, transplanted beneath the renal capsule of the rabbit, continued to grow and undergo endochondral ossification, maintaining their normal axial orientation. The naked cartilage block, after several days, induced the surrounding connective tissue to clothe its peripheral surface in the characteristic sheath of membrane bone that plays so prominent a part in the growth of cartilage bones. Far from limiting and directing the growth of the epiphysial cartilage, however, this periosteal sheath or ring of bone appeared to result

from some stimulus supplied by the growing cartilage itself.

Lacroix has demonstrated (in animals) a similar ring of periosteal bone which surrounds the periphery of the epiphysial plate at its junction with the metaphysial trabeculae. This region of the epiphysial plate was named by Ranvier (120) the "ossification groove"; Lacroix has called the bony sheath the "perichondrial ring of the ossification groove" and has ascribed to this region special properties of growth.

The "ossification groove" corresponds to the margin of the epiphysial plate where the most peripheral cells are massed together and merge imperceptibly with a profusion of connective tissue cells on the deep surface of the periosteum (or perichondrium). This is clearly shown in Figure 35, a photomicrograph of a section taken from the distal end of the femur of a two-year old child (see Material and Methods, Chapter III). That these connective tissue cells are "continuous with" the cartilage cells of the epiphysial plate is not disputed; whether this represents a transformation of peripheral cartilage cells into the cells of the proliferative layer of the periosteum, or whether periosteal cells add to the peripheral layers of the epiphysial plate and thereby increase its transverse diameter, has not yet been decided. Lacroix (90) subscribes to the latter view and is supported by Ham; (67); indeed, most histologists believe that the epiphysial plate increases its transverse diameter by appositional growth

FIG. 35

Photomicrograph of the most peripheral part of the epiphysial plate in a two-year old child. The immature cells of the resting and proliferative zones merge with the subperiosteal connective tissue.

from the overlying perichondrium (or periosteum). In the transplantation experiments already referred to, Lacroix found that transverse growth of the cartilage transplant was seriously retarded by removal of the peripheral region with the ossification groove. On the other hand, if the

denuded cartilage block was wrapped in periosteum before transplantation, a new ossification groove soon formed and transverse growth was considerable. Lacroix has crystallised the implications of these results in one sentence: "The presence and functioning of an ossification groove are indispensable to transverse growth of the epiphysial cartilage."

This contention has not remained unchallenged, Langenskiöld (91;92)has contributed some valuable work on the radiological features of dyschondroplasia (see Fig.17) which throws some light on the argument. According to him the epiphysial ends of the cartilage columns so characteristic of this disease tend to migrate peripherally over the years, indicating that the cells of the reserve zone of the epiphysial plate gradually progress in the same direction by interstitial growth, until ultimately they are transformed into the cells of the osteogenic layer of the periosteum.

In an attempt to elucidate this problem further, the epiphysial plate in the growing rabbit was examined autoradiographically after the administration of radioactive sulphur (S^{35}), as described in Chapter III (Material and Methods). Unfortunately, after the first 24 hours, most of the S^{35} activity occurs in the cartilage matrix outside the cells, so that no valid conclusions could be drawn about the pattern of cell division, although it was clear, even in these experiments, that the overall transverse width of the epiphysial plate had measurably increased after four or five days.

Far more successful experiments have been performed using tritiated thymidine (84; 121). Thymidine, a precursor of

desoxy-ribonucleic acid (D.N.A.), is taken up almost exclusively by dividing cells. By "labelling" it with tritium (a beta-emitting isotope of hydrogen), its presence in the nuclei of dividing cells can be detected autoradiographically after systemic injection. This method is ideally suited to a study of cell division in the growing epiphysial plate.

By adding tritiated thymidine to the culture medium, Rigal (1961) (121) has also studied cell division in post-foetal cartilage in vitro. Among other things he found that "endochondral proliferation is responsible for the increasing diameter of the epiphysial growth cartilage", thereby lending strong support to Langenskiöld's theory.

Both the above theories have been claimed to provide a pathogenetic basis for multiple exostosis. However, the best known of all these hypotheses, that of Keith (1920), depends for its validity on the presence of a controlling and directing sheath of bone - an extension of the diaphysial cortex - alongside the margins of the epiphysial plate. Keith based this concept on the radiographic appearances of tubular bones and did not present any histological evidence in support of this observation. The presence of this structure has been investigated with particular care by the author. Slab radiographs were prepared of the distal end of the growing femur in 14 subjects ranging in age from six months to 18 years (Material and Methods, Chapter III). Seven of these are shown in Figure 36; the age and sex are indicated in the original labelling of each radiograph. It is seen that the dense cortex thins down progressively towards the epiphysial plate and almost disappears at the most distal level. This is in keeping with what has been said about the

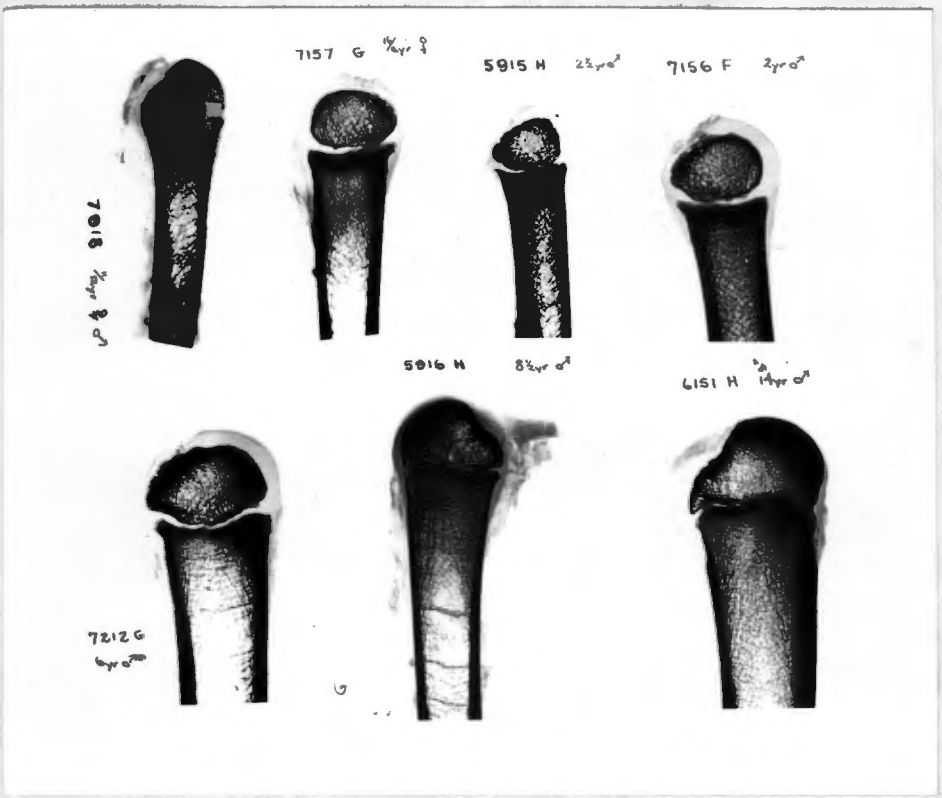
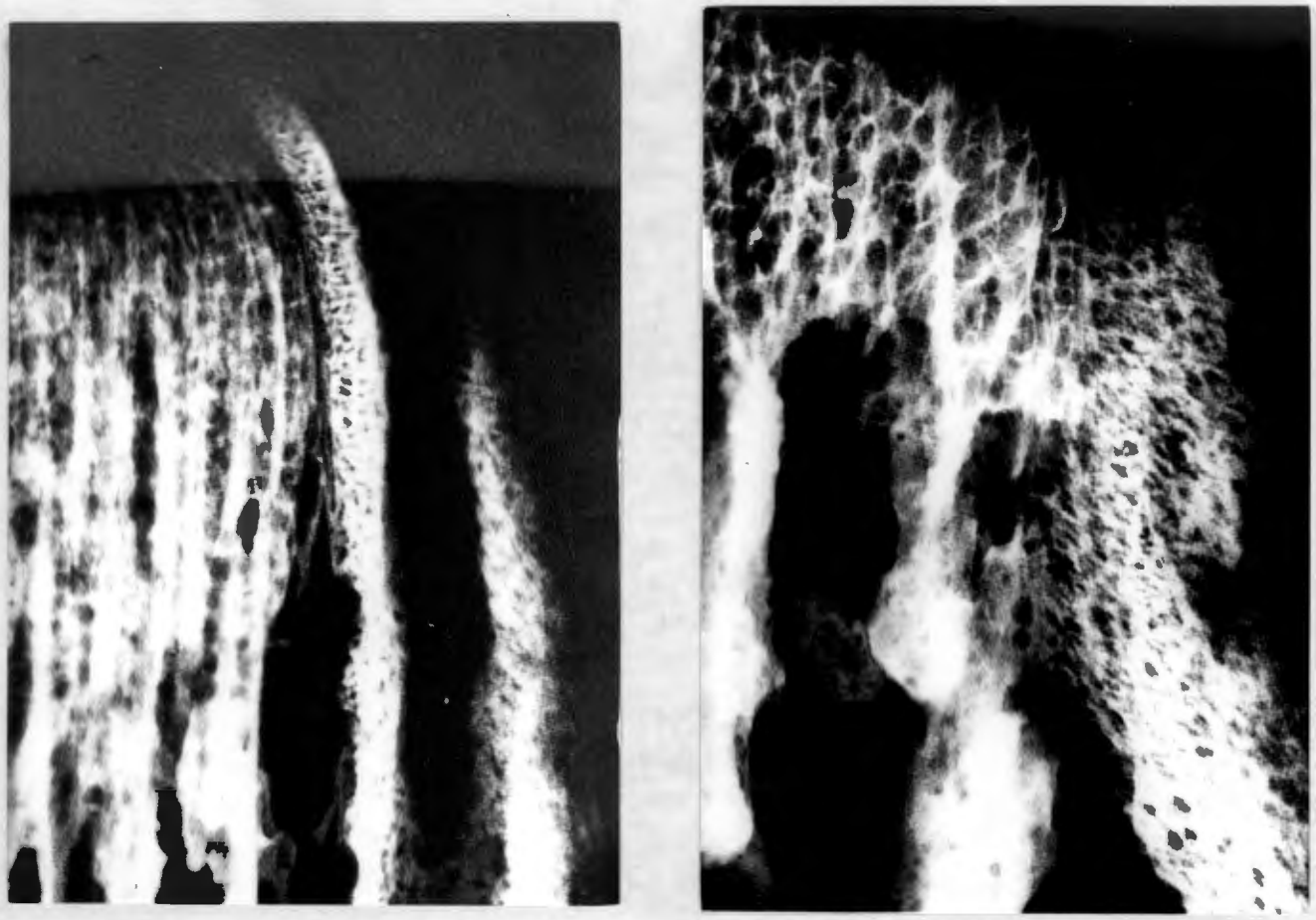


FIG. 36

Slab radiographs of the distal end of the femur.

resorption and modelling of the cortical bone adjacent to the epiphysial plate.

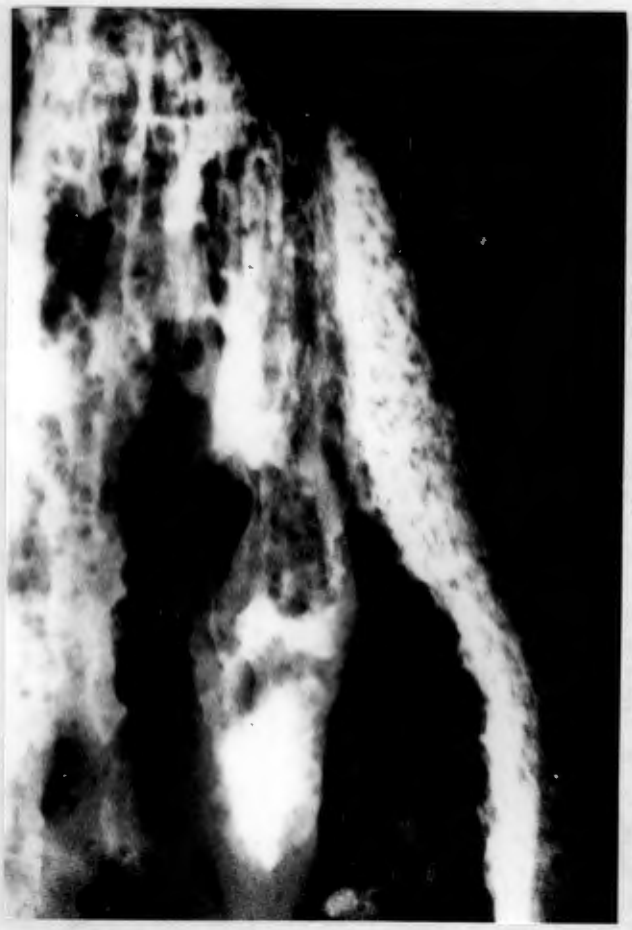
At microscopic level, however, there is a thin sheath of periosteal bone encircling the hypertrophic and calcified zones of the epiphysial plate - Lacroix's "perichondrial ring of bone" already referred to. It is seen in Figure 35 as a sliver of bone deep to the proliferative layer of the periosteum in this region; its presence is further confirmed by the microradiographs in Figures 37,a and b. These were prepared from specimens number 5915H and 7156 F, shown in Figure 36. They were obtained from two male children aged 2½ and 2 years, respectively. The sheath of periosteal (membrane) bone



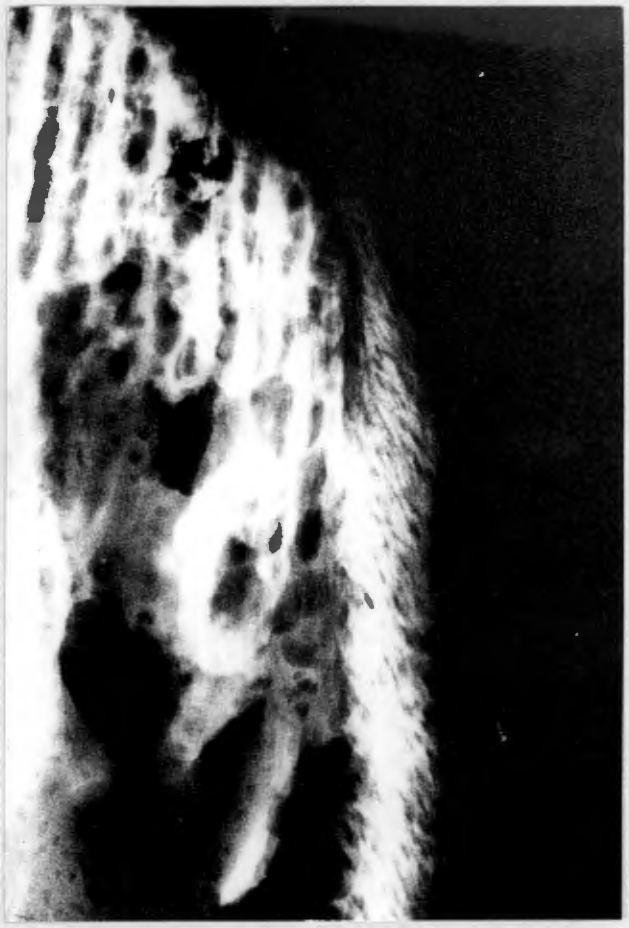
(a) (b)

FIG. 37

Microradiographs of the peripheral part of the epiphysial plate (the same area as that illustrated in Figure 35). The feathery looking radio-opaque columns to the left of the centre in each figure are due to new-formed trabeculae of bone. A sheath of periosteal (membrane) bone extends slightly beyond the metaphysial trabeculae in these specimens. Compare this with Figures 37, c and d , where the periosteal sheath of bone does not extend beyond the adjacent trabeculae.(see text).



(c)



(d)

FIG. 37, (c) & (d)

is clearly seen, extending slightly beyond the advancing trabeculae of the metaphysis. In older children and adolescents this periosteal bone was equally obvious but usually did not extend beyond the juxta-epiphysial trabeculae. Two such examples are seen in Figures 37,c and d; these microradiographs were prepared from specimens number 5916H and 6151H, shown in Figure 36. The ages of these two children were 8½ and 14 years respectively.

It is the author's contention that this sheath or ring is no more than the most advanced edge of that same periosteal sheath of bone which everywhere accompanies central, endochondral ossification. Where the fluted bone-end narrows down this sheath is eroded by osteoclastic resorption (see Fig.34), leaving only that segment of it opposite the widest part of the funnel. In experiments on ia rats, in which all osteoclastic resorption is inhibited, this ring is clearly shown to be continuous with the perichondrial and periosteal splint of the developing bone (13) Its role in the growth of transplanted epiphysial cartilage has been referred to above: Lacroix found that the periosteal sheath of bone was not essential for the normal orientation of epiphysial cartilage growth.

No evidence was obtained, therefore, of a controlling sheath or splint which normally limits epiphysial growth within strict confines.

Rate of Growth at the Bone Ends - Brief mention should be made of the work of the Bisgaards (1935), Gill and Abbott (1942)

and Lacroix (1951) (14; 58; 90) on the rate of bone growth. This has been supplemented by the clinical experiences of Green and Anderson (1947) with the method of epiphysial arrest for correcting inequality in limb length (60). It is today well known that the ends of the tubular bones contribute unequally to their growth in length; the proportionate contribution to elongation may be summarised in the following terms, after the work of the above authors :

PERCENTAGE CONTRIBUTION TO BONE LENGTH

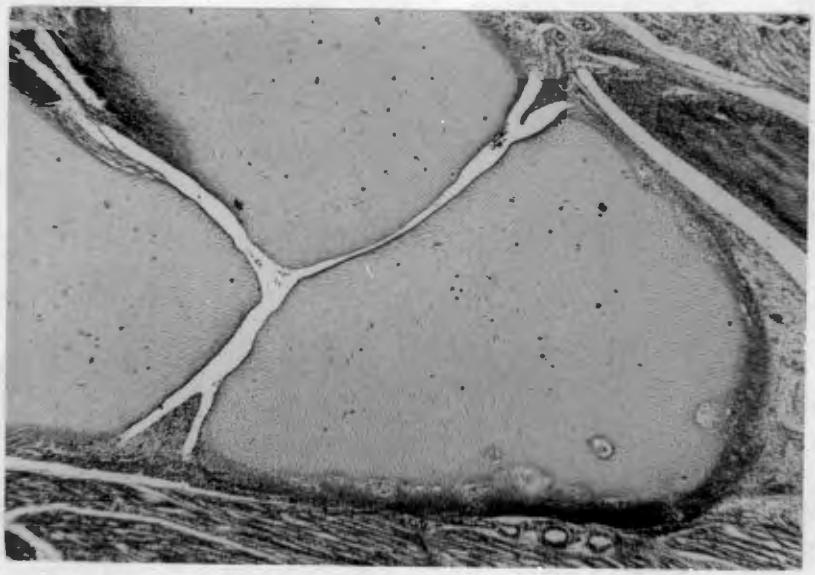
	FEMUR	TIBIA	FIBULA	HUMERUS	RADIUS	ULNA
PROXIMAL END	20	60	55	80	25	15
DISTAL END	80	40	45	20	75	18

THE GROWTH OF THE SMALL, IRREGULAR BONES.

Ossification of the carpal and tarsal bones usually does not begin until late in the foetal period or after birth. Until then the cartilaginous model increases slowly in size, mainly by interstitial growth but probably also by appositional growth from the perichondrium.

In the early foetal period - the third or the fourth month in the case of the talus or calcaneus - small blood vessels invade the model and give rise to the cartilage canals (Fig.38,a).

FIG. 38



(a)

Photomicrograph of a section through the tarsus of a twelve-week foetus. The cartilage canals have appeared. Ossification has not yet commenced. (x 20).

(b)

Photomicrograph of a section across the articulation between two tarsal bones in a growing child. The articular cartilage is now the only source of growth. (x 60).

Some months later the cells in the centre of the cartilage model begin to enlarge and then degenerate as the matrix becomes calcified. From the cartilage canals new blood vessels penetrate the degenerating cartilage and ossification follows. Unlike the tubular bones, this is not preceded or accompanied by periosteal new-bone formation, except possibly in the case of the calcaneus which later develops an epiphysial plate.

From the centre of the model, ossification proceeds in all directions simultaneously, though with due regard for the irregularities of shape to be encountered. When it reaches the surface, periosteal bone formation commences and from then on further growth at these surfaces is by appositional growth. Only at the articular surfaces of these irregular bones does cartilage persist, and here endochondral ossification proceeds as in tubular bones, though at a greatly diminished level (Fig.38,b). It is important to realise that in these bones the ultimate shape, the intricacies of contour and angular relationships, are present in the cartilage model before ossification starts. This has been well described in the case of the talus (Gardner, 1956): Broadening and increase in vertical height occur just after the fourth month of intra-uterine life; a gradual change in the medial angulation of the neck takes place from the fourth month until after birth, yet still during the purely cartilaginous phase. Thus there is no need for the extensive modelling processes so characteristic of tubular bones. Furthermore, cartilage growth and endochondral ossification proceed centrifugally in all directions

at more or less equal rates - there is no "elongation" of the bone and therefore no need for the continual osteoclastic resorption of the growing end described in the section on tubular bones.

These differences are stressed because they appear to the author to be fundamental in explaining the unusual distribution of the lesions in multiple exostosis, which are seldom seen in the carpal and tarsal bones. This will be discussed in a later chapter.

OSSIFICATION OF THE CLAVICLE.

The clavicle is generally thought of as a membrane bone, yet cartilage-capped exostoses are not uncommon at the sternal and acromial ends.

The development of the clavicle has been studied in detail by Fawcett (1913), Hanson (1920), Todd and D'Errico (1928) and Noback and Robertson (1951) (48;68;110;139).The blastemal condensation is recognisable at a very early stage and direct, intramembranous ossification commences from the 15 mm. stage onwards (the sixth or seventh week of intra-uterine life). Starting as two separate centres, these soon fuse and ossification extends towards the acromial and sternal ends of the bone. Before it is complete, however, the tissue at the bone ends is converted to precartilage and later true cartilage. From this stage onwards the bone extends in length by endochondral growth and ossification at the sternal and acromial ends, accompanied (as in the long bones) by

osteoclastic resorption and modelling. There is no true epiphysial plate and the orderly columnation of cartilage cells is absent. By the end of the foetal period these zones constitute little more than the articular cartilages, but growth still proceeds and is not completed until after the twentieth year of life (59).

It is seen, therefore, that the sternal and acromial ends of this bone are truly endochondral and it is not surprising that exostoses are found at these sites. Furthermore, the absence of an epiphysial plate, as such, is of little importance, for it will be shown that the clavicle is more frequently involved than the distal end of the humerus or the proximal ends of either the radius or ulna. What is important (and what has been stressed throughout this chapter) is the preosseous tissue in which the bone is formed and the manner of growth at the particular site.

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CHAPTER XIV.

THE EVOLUTION OF THE LESIONS IN MULTIPLE EXOSTOSES.

The initial deviation from normal bone growth is unrelated to any precipitating factor and may occur at any time from birth (or possibly even earlier) to the end of the growth period for that particular bone. Thus, normal growth may precede and follow a starkly abnormal interlude (Fig. 39); or new exostoses may appear after intervals of normal growth (Fig. 45). However, in spite of the persistence of subperiosteal islets of cartilage cells in adult bones - a phenomenon referred to in Chapter VIII - there was no instance, in the present series, of a new exostosis arising after the cession of growth, nor has this been recorded in the literature, except as a manifestation of malignant neoplasia.

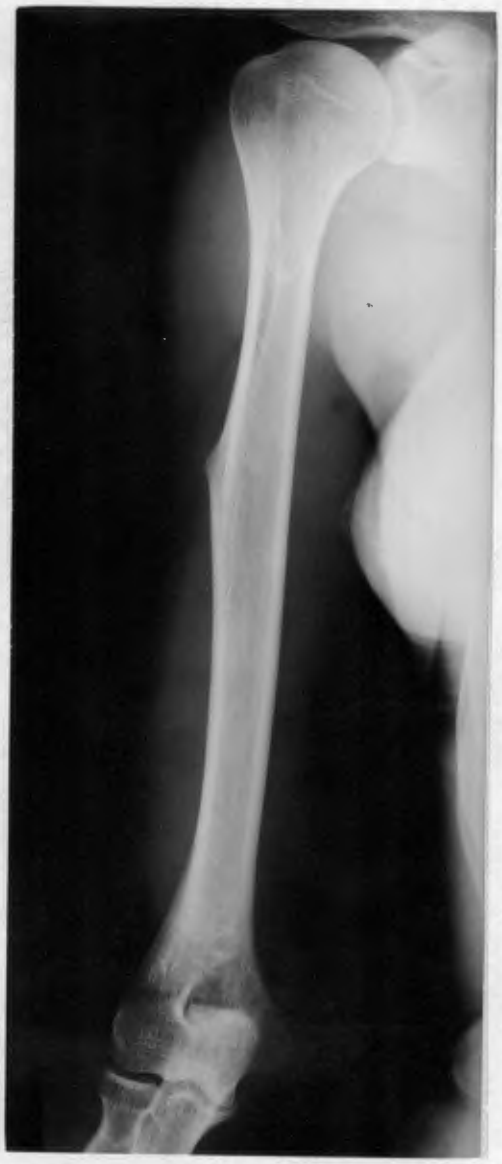
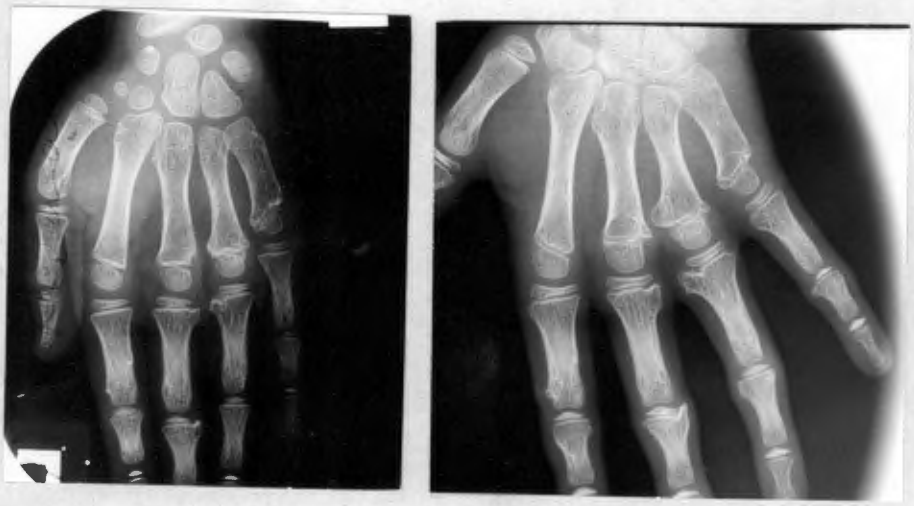


FIG. 39

An exostosis of the shaft of the humerus, preceded and followed by normal bone growth.

The earliest radiologically detectable lesion is an asymmetrical or beaked overgrowth of the cortex immediately adjacent to the epiphysial plate (Fig. 40,a). At a slightly later stage this new dimension has become the pattern of growth at that site, either in the shape of a broadened metaphysis (Fig. 40,b) or, equally characteristically, as the base of attachment of a freely growing exostosis (Fig. 41).



(a) (b)

FIG. 40

Radiographs of the hand at successive ages showing exostoses in various stages of development.

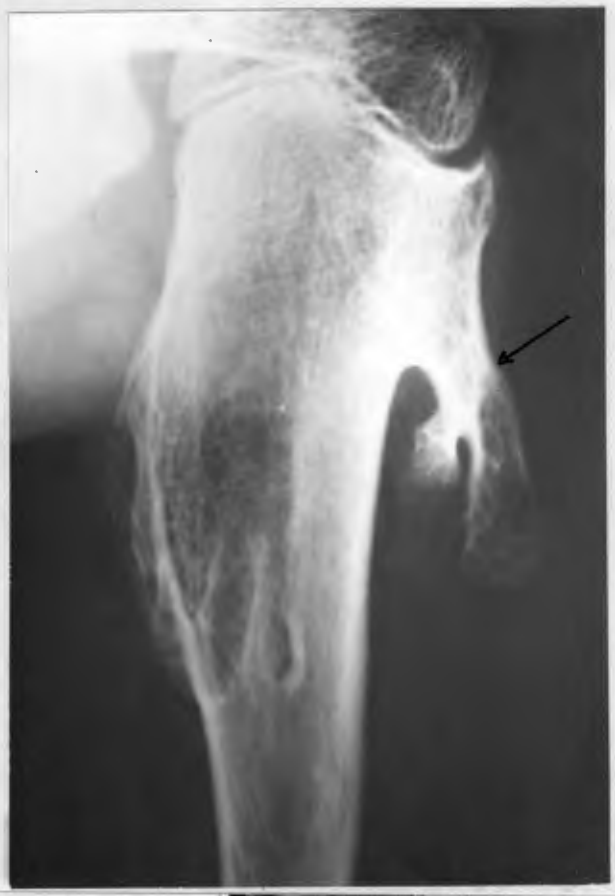


FIG. 41

Radiograph of the proximal end of the humerus. There are several exostoses; the one on the lateral aspect of the bone is discussed in the text.

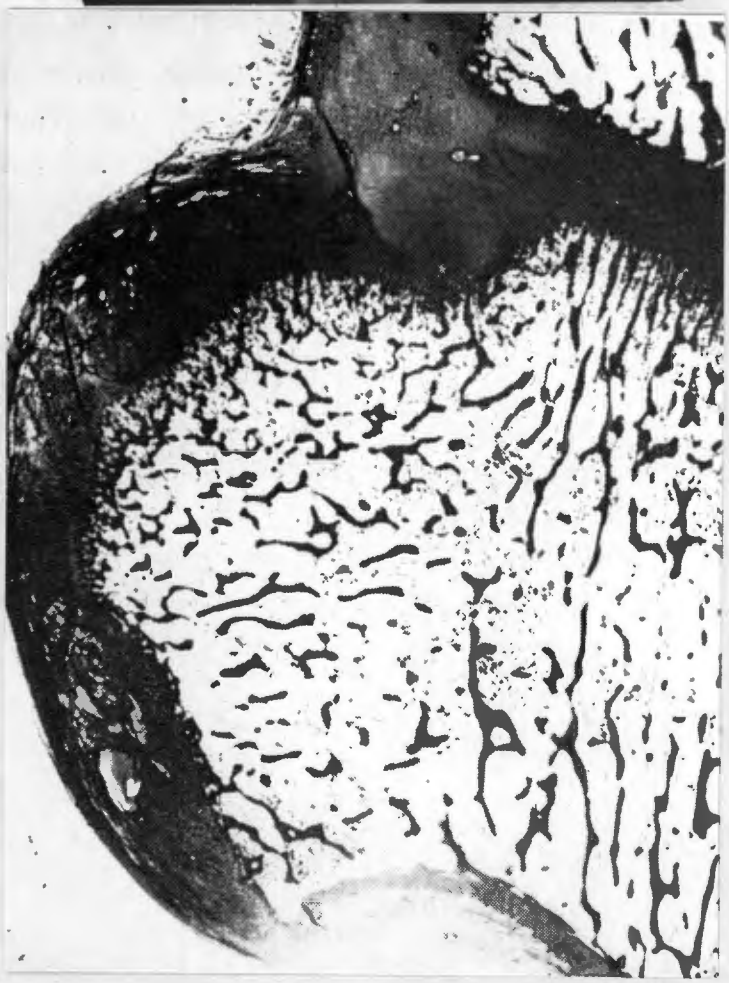


FIG. 42

Photomicrograph of an exostosis with the cartilage cap in direct continuity with the epiphysial plate. (Reproduced from Anderson's Pathology).

The last figure bears close examination: the base of the exostosis is continuous with the bone most recently formed by the epiphysial plate at the proximal end of the humerus; more medially the new-formed bone extends into the diaphysis and the exact junction of the "exostotic" and the "normal" bone is impossible to define. Cortex and juxta-epiphysial trabeculae are confluent between the metaphysis and the exostosis. In pictorial terms, the bone-work of the exostosis appears to have flowed out from the same source as that of the spongy metaphysis, namely the cartilaginous epiphysial plate. The histological counterpart of this process has been observed in early, cartilaginous exostoses. Fig. 42, reproduced from Anderson's Pathology, shows the young cartilaginous outgrowth clearly in continuity with the epiphysial cartilage. Taken together, the evidence presented leaves little doubt that the cartilage-capped exostoses in this disorder arise from the proliferative, peripheral regions of the growing cartilage.

From the neck of the exostosis onwards there is a change in the character of the bone. This point, indicated by an arrow in Figure 41, marks the junction and attachment of two separate "buds" of bone, much more delicately trabeculated than the base of the exostosis. It seems likely that the bone distal to the arrow is derived from the cartilaginous cap of the exostosis. It takes little

imagination to picture this cartilaginous element carried out during the initial evolution of the lesion and then commencing to grow in its own right, with its own sequence of ossification, adding the delicate spongework which now makes up the bulk of the exostosis.

The future pattern of growth is quite unpredictable when exostoses first appear. The juxta-epiphysial projection may be followed by normal growth leaving an isolated exostosis jutting from the diaphysial shaft; or else the asymmetrical increase in width may be established as the new model for further growth and new bone, irregularly heaped into a broad metaphysis, produces the characteristic club-shaped appearance of the bone end. Figures 43 and 44 show the progress of the disease in one child over a period of ten years from the age of three to thirteen. The earliest exostosis at the proximal end of the humerus appeared during the same year as the exostosis at the distal end of the radius.

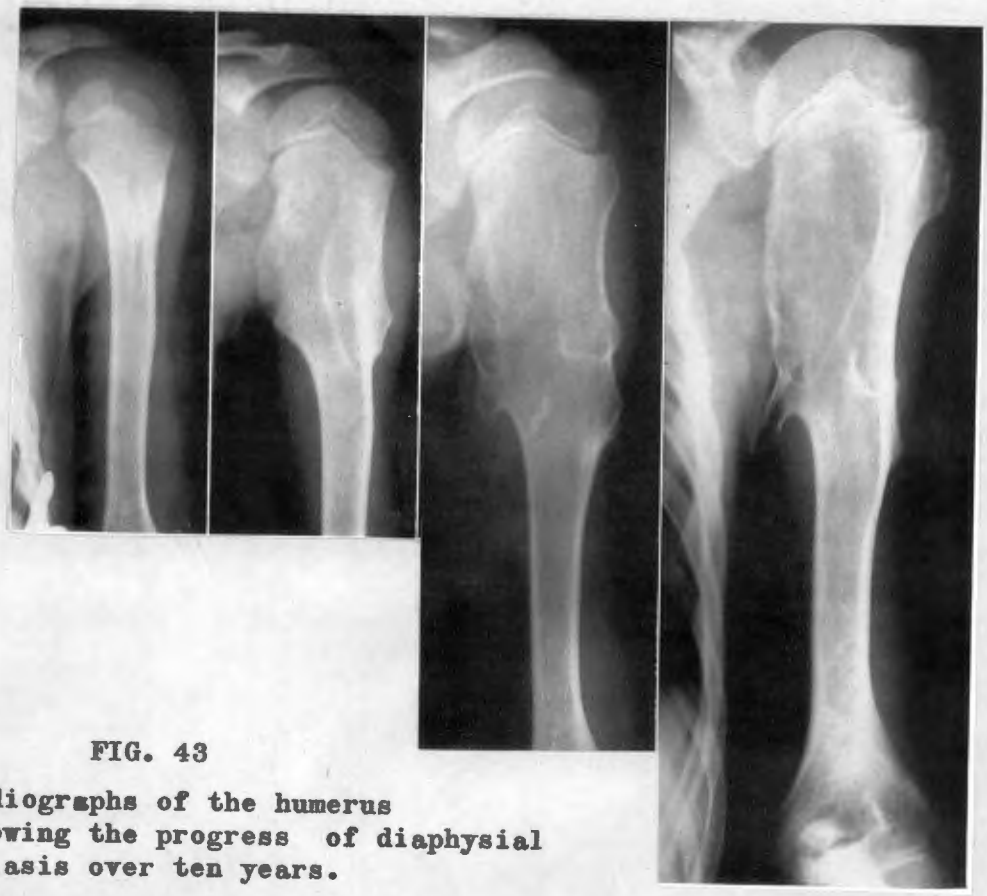


FIG. 43

Radiographs of the humerus showing the progress of diaphysial aclasis over ten years.

During the next ten years of growth the proximal end of the humerus has continued to grow in its new, grossly abnormal mould with considerable shortening, while over the same period all further growth of the distal end of the radius has been absolutely normal and at the age of 13 the original exostosis is hardly recognisable half way along the shaft of the bone (Fig. 44).

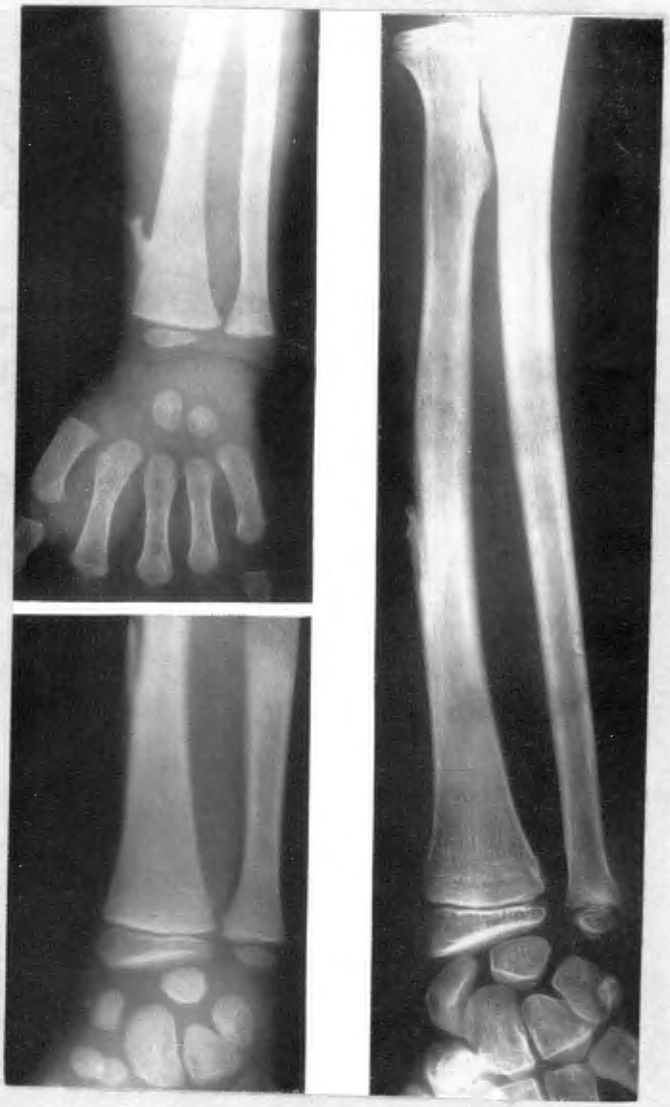


FIG. 44

Radiographs showing the radius and ulna in the same patient as Figure 43.

There is no way of telling, in any particular child, which of these patterns will unfold, nor is it certain that any potential site will develop an exostosis at all. A careful search, among the 39 families studied, for intrafamilial resemblances in the form of the disease, revealed only one family in whom all the affected members had similar lesions (Pedigree No. 34). This family is discussed in more detail in the section on Heredity.

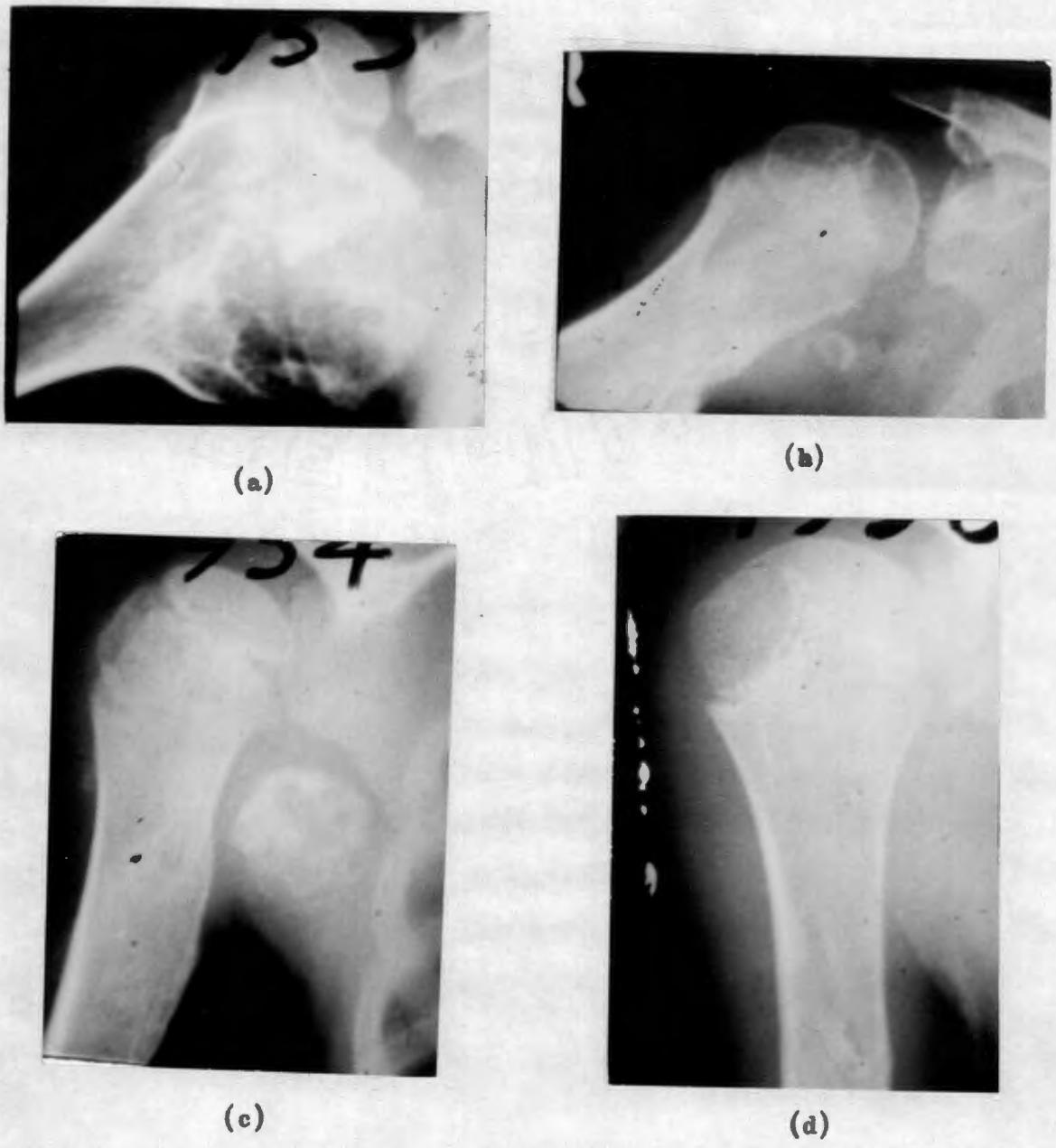
For the rest the abnormality appears to manifest itself as a completely isolated phenomenon each time it occurs, varying not only from patient to patient but from one bone to another in the same patient and even within the same bone at different times (Fig. 45).

FIG. 45

Different types of lesion affecting the femur at different times, with intervening periods of apparently normal growth.

Once formed, its cartilage cap lends to the exostotic mass an existence and a growth potential of its own, even assuming, in some measure, a competitive relationship with the parent bone. The independent capacity of this cartilage, which (in the opinion of an authority such as Willis (152) is still not neoplastic, is vividly illustrated by the following case (Pedigree No: 14, III, 3).

The patient was first seen at the age of five years and found to have multiple exostosis. A large protrusion



(a) (b) (c) (d)

FIG. 46

Exostosis of the proximal end of the right humerus. Incomplete removal of the lesion resulted in a recurrence in the form of an osteocartilaginous ball in the soft tissues of the axilla.

at the proximal end of the right humerus, which interfered markedly with shoulder movement, required surgical excision (Fig.46,a). The exostosis was removed with difficulty and a radiograph one month after operation showed a small osteocartilaginous fragment left behind in the soft tissues near the raw bone surface (Fig.46,b). Two years later it had grown to the size (and shape) of a walnut, about two centimetres in its greatest diameter, quite separate from any bony attachment whatever (Fig. 45,c)! The ossified ball was removed and, four years later, there was no evidence of any recurrence (Fig. 46,d).

During the normal period of growth the exostoses may continue to enlarge, assuming an abundant variety of sizes and shapes, from the tiniest spike on a metacarpal or phalangeal bone to a cauliflower-like mass of huge dimension on the femur or pelvis. These appearances are illustrated in the many radiographs reproduced here. In all these films a certain characteristic distribution of the lesions will haye been recognised, which calls for closer examination and elucidation.

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CHAPTER XV.

DISTRIBUTION OF THE LESIONS IN MULTIPLE EXOSTOSIS.

The dominance of the cartilaginous element in the development of the exostosis, from its inception to the full-blown form, points clearly to its origin. This is a disease of the endochondral skeleton and the lesions, however abundant, are strictly limited to those bones developed in cartilage. The detailed distribution is characteristic, and was well recognised a hundred years ago by Virchow (145) and Weber (150) (Fig. 47). Beside this beautiful illustration, reproduced from Weber's paper (1866), is tabulated the number of patients in the present series in whom each site was found to be involved. These data were obtained from complete radiographic surveys of 76 subjects (See Chapter III, Material and Methods). No comparative figures are listed, as there is no record of any large series of cases subjected to detailed radiographic examination. However, the figures correspond roughly with the findings of Jaffe (76), Dahlin (30) and Stocks and Barrington (135).

Either the distal end of the femur or the proximal ends of the tibia and fibula were affected in almost every patient examined. All the tubular bones were frequently involved and the iliac crests, the vertebral borders of the scapulae and the ribs were the next most commonly affected sites.

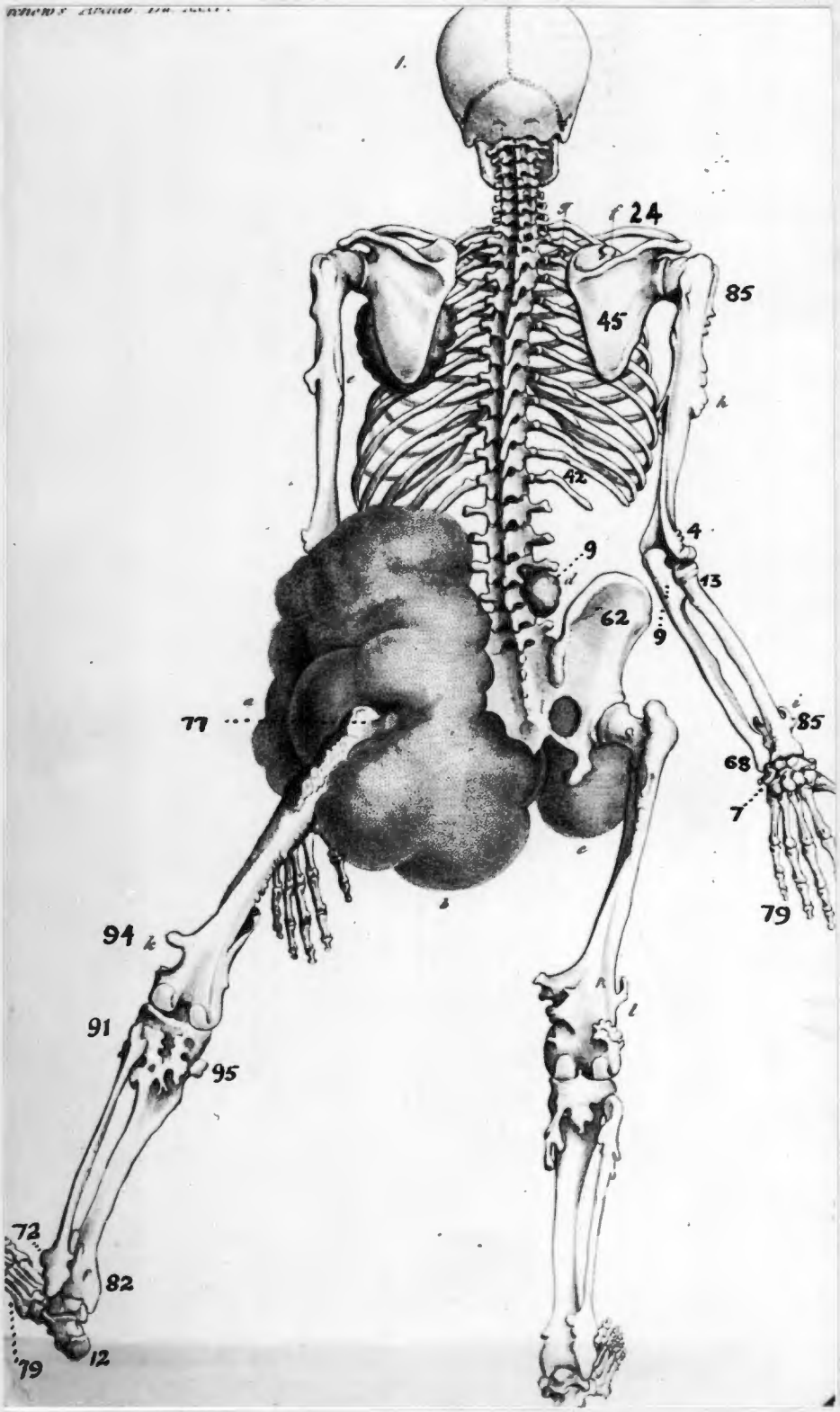


FIG. 47

Distribution of the exostoses in fifty-two index patients and twenty-four affected relatives. Data obtained from complete radiographic survey of the seventy-six subjects. Numbers are expressed as percentages.

The clavicle, contrary to the findings of Stocks and Barrington (135) was affected in no less than 18 (24 per cent) of these patients. Jaffe (1943) (76) mentions the occurrence of exostoses on this bone, but the lesions which he described were tiny osteocartilaginous buds situated mainly at the sternal end of the bone. Tiny exostoses of this type were encountered in the present series as well, but the usual clavicular lesion was a craggy exostosis, 1-3 centimetres in diameter, at the acromial end of the bone (see Fig. 14).

The vertebral bodies were rarely affected, and then only showed the tiniest exostoses, related to the proximal or distal epiphysial disc. In six of the seven patients affected the exostoses occurred at the tips of the spinous or transverse processes (Fig. 15).

The calcaneum was unequivocally involved in seven patients and some other tarsal bone in two. A carpal bone showed some detectable lesion in five patients (Fig. 48).

The sternum was only once found to be involved and the patella not at all.

In all this, a pattern begins to emerge, namely, that the bones with the largest growth potential are more commonly involved than the others. Furthermore, in the tubular bones the more actively growing end is invariably affected with greater frequency and greater severity than

the less active end (Table X).

TABLE X

THE RELATIONSHIP BETWEEN RATE OF GROWTH AND FREQUENCY OF EXOSTOSES (SEVENTY-SIX CASES).

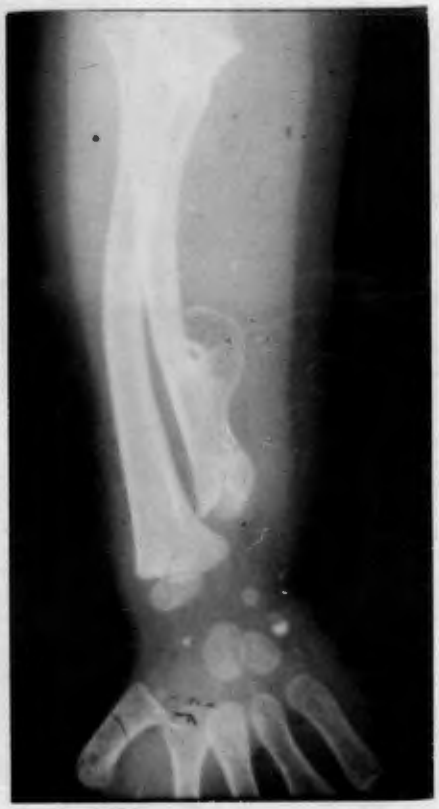
Bone	Proportionate contribution to bone length (expressed as a percentage of total elongation)		Number of cases affected	Percentage of total
Femur	Proximal end	20	58	77
	Distal end	80	71	94
Tibia	Proximal end	60	72	95
	Distal end	40	62	82
Fibula	Proximal end	55	69	91
	Distal end	45	55	72
Humerus	Proximal end	80	65	85
	Distal end	20	3	4
Radius	Proximal end	25	10	13
	Distal end	75	64	85
Ulna	Proximal end	15	7	9
	Distal end	85	52	68

Neither this predilection for the "growing ends" of the long bones, nor the peculiar rarity of exostoses in the carpal and tarsal bones, have been satisfactorily explained.

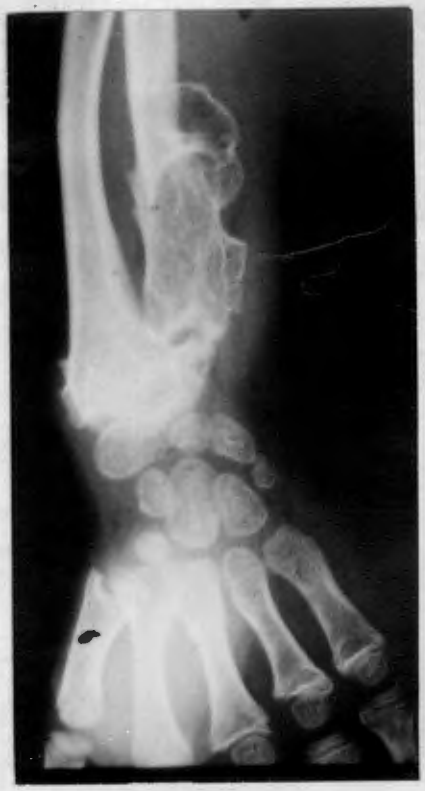
Radiographic examination of representative sites at successive ages in 41 subjects has shown that this selective distribution within the endochondral skeleton may be less a peculiarity of the disease than a reflection of certain differences in the normal process of growth at the different sites. It is remarkable that the distal end of the humerus and the proximal end of the ulna, where the epiphysial plates contribute very little to bone

length (see Chapter XIII), are affected by exostoses in only four per cent and nine per cent of cases, respectively - no more frequently, in fact, than a tarsal bone such as the calcaneum which also develops an epiphysial plate and grows slightly in length after the main body of the bone has been ossified - showing that it is neither a quality of tubular bones as such, nor even of those regions with epiphysial plates, to develop exostoses with notable frequency.

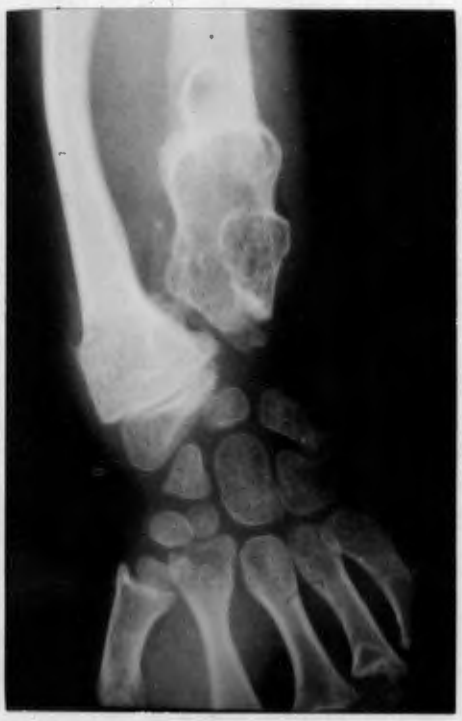
The other tarsal and carpal bones very rarely show obvious lesions in routine radiographs. However, when the development of these bones is traced by serial radiographs at successive ages, abnormalities of growth can be demonstrated at some stage in at least half of the patients so examined. A typical case is illustrated in Fig. 48,a,b,c,d. At five years two unusually dense ossification centres appeared - one in the triquetrum and another in the scaphoid. Four years later these two bones had developed miniature exostoses and the distal pole of the triquetrum was clearly abnormal in size and shape. Thereafter, as growth proceeded, centrifugal ossification appeared to overtake these bony irregularities, gradually obscuring them in later radiographs. A single radiograph taken at the end of growth will probably show no sign at all of these early abnormalities.



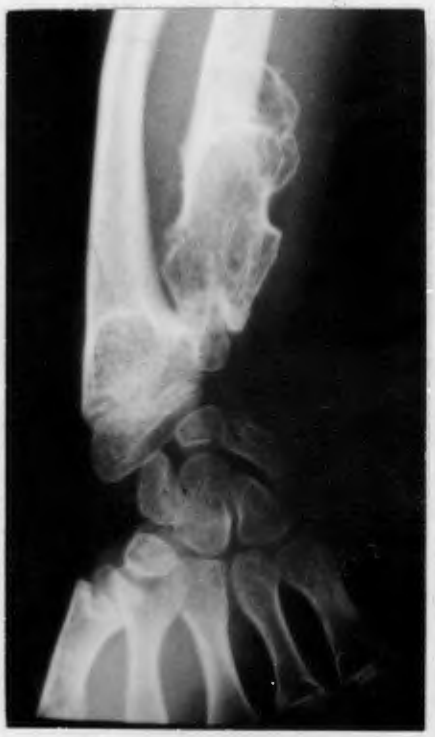
(a)



(b)



(c)



(d)

FIG. 48

Radiographs of the wrist taken at five, nine, ten and twelve years of age. The earliest film showed two unusually dense ossification centres in the bones which later developed miniature exostoses.

Only the carpal bones have been studied in this way; it seems likely that the other small bones behave similarly. They have this in common, that growth and ossification proceed in all directions from the centre. Consequently there is no elongation of the bone, no marked transport of the growing end from its original position relative to the primary centre of ossification, no extensive modelling process - all characteristic features of growth in tubular bones. The presence or absence of an epiphysial plate as such is not important. The vertebral bodies, which develop two annular epiphysial centres at the upper and lower surfaces, are extremely rare sites of the disease, while the distal ends of the phalangeal bones, where there are no epiphysial plates, often have exostoses (Fig. 14).

On the basis of these observations it is suggested that all the bones developed in cartilage are equally exposed to the genetic disorder in hereditary multiple exostosis. The development of detectable lesions, however, is largely determined by the degree of elongation and modelling which the bone undergoes during growth; these factors are reflected in the characteristic differential incidence of lesions at the various sites.

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C H A P T E R XVI.

BONE GROWTH IN DIAPHYSIAL ACLASIS.

INTRODUCTION.

In the previous chapters it has been shown that the evolution and the distribution of the lesions in diaphysial aclasis are intimately related to the processes of endochondral growth and ossification. It is here, in the mechanism of growth, that the basic abnormality lies, manifesting itself in the widespread deformities of the appendicular skeleton.

Some of these deformities, and in particular the shortness of stature, were observed and described during the first half of the 19th century (134). Yet, with few exceptions, the published accounts of the disease from then on, to the most recent times, have revolved around the exostoses with only vague references to the growth disorder.

John Hunter's belief that the condition of exostosis was "constitutionally interwoven with the formation of bones in such people" (73) was echoed 133 years later by Sir Arthur Keith when he first encountered the disease (83) Above all he was impressed by the abnormality of growth, indeed, urged that the condition be removed altogether from the

category of "tumours" to be placed among the "disorders of growth" and, to this end, adopted the name diaphysial aclasis, suggested to him by his friend Morley Roberts. In spite of this, bone growth in diaphysial aclasis has received scant attention and, until the findings of the present study were published in 1961 (132) there were no detailed anthropometric data available concerning this disorder.

The methods used here and the standards employed were described in Chapter III (Materials and Methods). In addition to the primary abnormality of growth, the secondary effects due to the presence of exostoses were investigated as well. The findings are presented under three main headings :

(1) Abnormal bone growth:
   (a) retardation of bone growth;
   (b) adaptations of bone growth due to pressure by adjacent exostoses.

(2) Migrating exostoses.

(3) Disappearing exostoses.

Acknowledgment. Most of the material used in this chapter appeared in a paper by the author in the Journal of Bone and Joint Surgery (Solomon, L.: "Bone Growth in Diaphysial Aclasis." J.Bone and Joint. Surg., 1961, 43B, 700). Figures 49-53 and 56-67 were reprinted from the same article.

1. ABNORMAL BONE GROWTH

The patient shown in Figure 49 presented simultaneously all the deformities encountered in diaphysial aclasis. Though by no means a dwarf he had the characteristically short stature, being 157 centimetres in height. The left forearm, in addition to being short, showed bowing of the radius, ulnar deviation of the wrist due to a short ulna, and dislocation of the radio-humeral joint. The left hand was broad and stubby, the fingers shorter than those of the right hand. There was genu valgum on the right side and a valgus deformity of the right ankle. There was a mild though definite thoracic scoliosis with vertebral rotation. On radiographic examination the pelvis was distorted and there was bilateral coxa valga. All these deformities, either singly or in varying combinations, have been described before, but there were two further deformities that do not appear in the literature on the subject. Firstly, the left clavicle was clearly diminished in length compared with the right side and on measurement was almost two centimetres shorter than

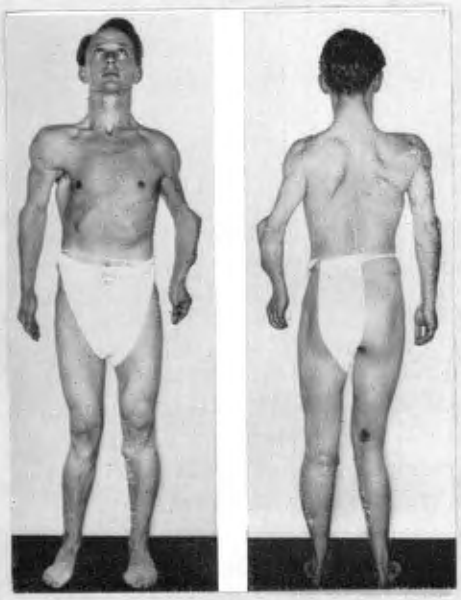

FIG. 49
The deformities associated with diaphysial aclasis.

the right. This gave rise to the asymmetrical appearance of the pectoral girdle. Secondly, the thoracic cage under the right scapula presented a gentle indentation where it had moulded itself to a large exostosis on the deep aspect of the scapula (Fig. 50).

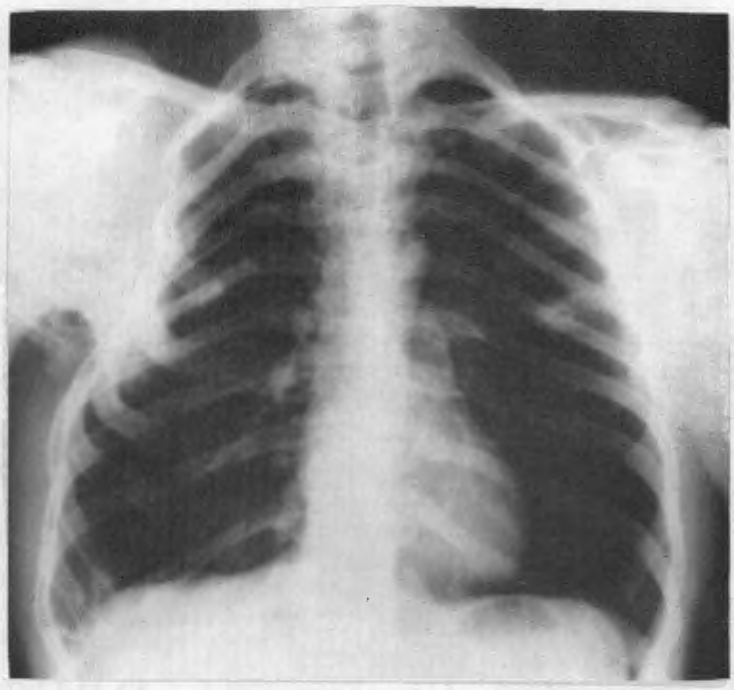

FIG. 50

Radiograph showing deformity of the thoracic cage on the right side.

Incidence and distribution of deformities - Bony deformities of one sort or another (as distinct from exostoses) were encountered in 56 of the 76 patients examined in detail, and were distributed equally as to sex (Table Xl). These 56 patients were analysed in greater detail and the occurrence of individual deformities is shown in Table XII. No attempt has been made to present figures for conditions like shortening of the clavicles and coxa valga which are in most cases difficult to assess.

TABLE XI

INCIDENCE OF DEFORMITIES IN SEVENTY-SIX PATIENTS WITH DIAPHYSIAL ACLASIS

Sex	Multiple exostoses	Associated deformities	Percentage with deformities
Males . .	36	26	72
Females .	40	30	75
Total .	76	56	73·7

TABLE XII

DEFORMITIES PRESENT IN SEVENTY-SIX PATIENTS WITH DIAPHYSIAL ACLASIS

Deformity	Number of patients				Percentage
	Both sides	Right side	Left side	Total	
All forearm deformities .	15	8	14	37	50
Bowed radius . . .	13	7	13	33	43
Conical ulna . . .	5	6	8	19	25
Radio-humeral dislocation	1	2	3	6	8
Genu valgum . . .	7	3	6	16	21
Valgus ankles . . .	29	4	1	34	45
Deformities of the hands .	6	3	4	13	17
Short stature . . .	—	—	—	31	41
Scoliosis . . .	—	—	—	3	4
Pelvic deformities . .	—	—	—	3	4
Thoracic deformities .	—	—	—	2	3

Of all these characteristic deformities only the valgus ankles have any clear tendency to be symmetrical. The others are scattered haphazardly in one limb or another, though there is some relationship to the number and size of the exostoses affecting the particular region. When a bone is free from any exostosis an associated deformity is rare.

(a) RETARDATION OF BONE GROWTH.

All the deformities of the tubular bones can be explained in terms of the same common factor: diminished length of the bones affected by the disease. A closer look at the individual deformities will illustrate this point.

Deformities of the forearm and wrist - One or other of the characteristic forearm deformities occurred in almost half of the patients examined, though the more marked manifestations such as radio-humeral dislocation were comparatively uncommon. Figure 51 shows the radiographs of one such patient. The radius is bowed throughout its length, not merely at the distal end where exostoses are common. Moreover, the left radius is bowed though this bone has no exostosis at all.

The gravest effect here is obviously the gross shortening of the ulna. Even when both bones are equally affected by exostoses the ulna is almost invariably more severely shortened than the radius. This growth deficiency is confined to the distal end of the bone, which is typically carrot-shaped; the radio-ulnar joint is often disrupted and the wrist deviated to the ulnar side.

There are at least two reasons for this disproportionate shortening of the distal end of the ulna. Exostoses are rare at the proximal end of either the radius or the

ulna, whereas the distal ends are affected in 85 and 68 per cent of cases respectively. This is in keeping with the general observation that the bone ends which contribute most to the total diaphysial length are the more frequently affected in diaphysial aclasis (Table X). Although it is almost impossible to determine the exact proportionate contribution of proximal and distal ends to total bone length (indeed, it varies quite widely from person to person), it seems certain the distal end of the ulna contributes more to total bone length than the distal end of the radius. Equal involvement of these two bones at more or less the same age can therefore be expected to cause a greater diminution in the ultimate length of the ulna than of the radius.

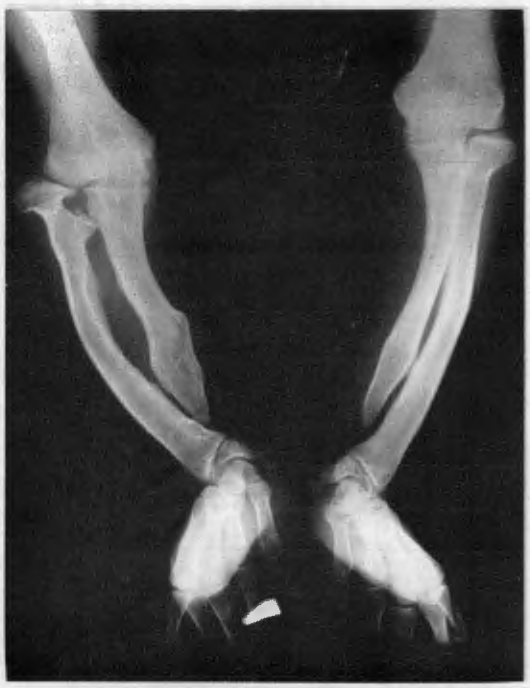

FIG. 51

Radiograph showing the characteristic forearm deformities. The ulna is short and tapered at the distal end; the radius is bowed and there is subluxation of the right radio-humeral joint.

The second possible reason for this undue shortening of the ulna is the difference in cross-sectional area of the epiphysial plates of the two bones, the ulnar plate being less than a quarter the area of the radial plate. "Equal" involvement by exostoses, therefore, means greater proportionate involvement of the ulnar growth plate. Whatever the ultimate mechanism may be, there is evidence that the retardation of growth is related to the extent to which the particular epiphysial plate is disturbed by the disease.

The result of this disproportionate ulnar shortening is that the radius, tethered firmly to the ulna and growing considerably more than the latter, is accommodated in one of two ways; either it bends or there is dislocation of the radio-humeral joint. When dislocation occurs the bowing is less than would otherwise be expected (Fig. 52).

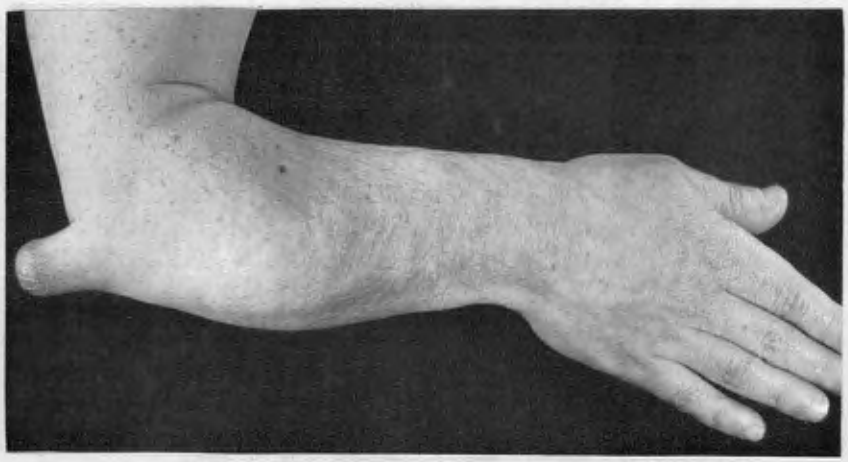

FIG. 52

Dislocation of the radio-humeral joint. The projection at the elbow is not an exostosis; it is due to the proximal end of the radius which has been dislocated since childhood.

Valgus deformity of the knee and ankle. Genu valgum of more than moderate degree occurred in 16 of the 76 patients. Obliquity of the tibial articular surface with valgus tilting of the talus occurred in 34 of the 76 patients, and of these all but five were bilateral and symmetrical. The defect underlying these deformities is similar to that in the forearm: disproportionate shortening of the fibula as compared with the tibia. The structure of the knee joint, however, in which the fibula does not articulate with the femur, ensures that tibio-femoral dislocation will not occur (cf. radio-humeral dislocation at the elbow). Instead, the proximal end of the tibia, or the knee joint itself, may be distorted into the valgus position (Fig. 53).

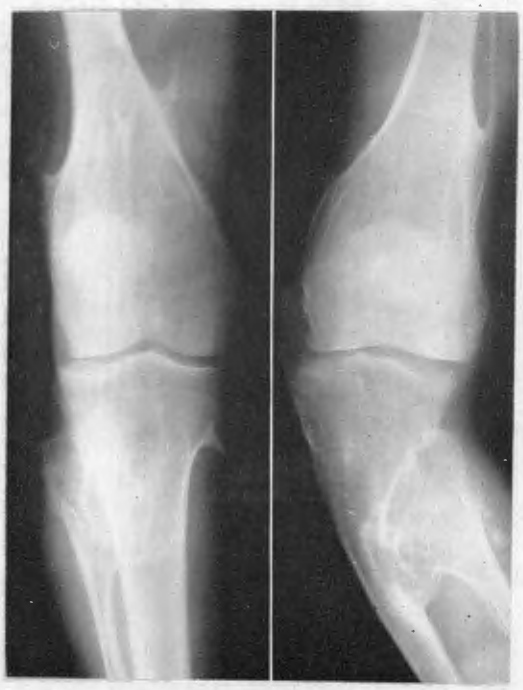

FIG. 53

Radiograph showing genu valgum from bowing of the tibia.

More often the effects of the shortened fibula fall upon the ankle where the tibial articular surface is tilted obliquely towards the fibula (Fig. 54).

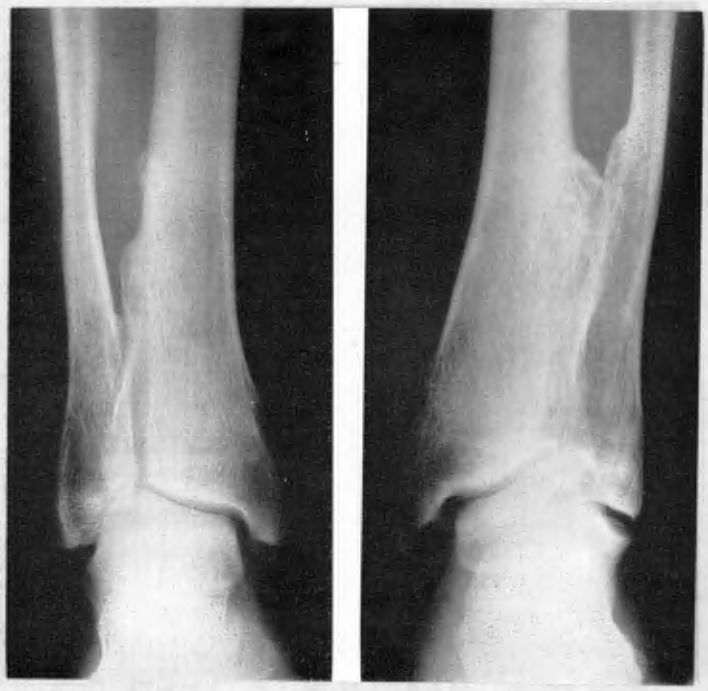

FIG. 54

Radiographs showing valgus deformities of the ankles. Note that in spite of a marked tilting of the tibial articular surface the line of the epiphysial plate is horizontal.

It is important to notice that the lower epiphysial plate of the tibia remains horizontal; it is not distorted except in the most severe cases, and even then the horizontal disposition is retained though the lateral part of the articular surface is forced right into the metaphysis.

The valgus deformity is almost entirely a

deformity of the tibial epiphysis, which is wedge-shaped in all these cases. The disproportionate shortening of the fibula causes the lateral malleolus to lie at the same level as - and sometimes higher than - the medial malleolus, though still retaining its strong attachment to the tarsus through the ligaments of the ankle joint. The talus is thus tilted into valgus and drawn up hard against the lateral part of the tibial articular surface, which increasingly bears the stress due to the disproportionate tibial growth. Growth of the tibial epiphysis, which is derived almost entirely from the articular cartilage, is thus interfered with mainly in its lateral half, with consequent wedging of the epiphysis. If the deformity were due to unequal growth at the tibial epiphysial plate, this plate would itself be tilted and distorted obliquely, and this has been shown not to occur. So, once again, the inescapable conclusion is that the deformity is the result of diminished bone length, the "short bone" in this instance being the fibula.

Shortening of the clavicle - Like other bones affected by multiple exostoses, the clavicle may be shorter than usual (Fig. 49). It remains only to comment on the fact that this bone should be affected at all. Regarded by many as a membrane bone, it was at one time thought not to be involved in diaphysial aclasis - a disease of the bones preformed in cartilage. Routine radiographs, however,

show that the clavicle is involved in 24 per cent of patients with this disease, usually at its acromial end, but sometimes also at its sternal end.

The development of the clavicle was discussed in some detail in Chapter XIII where it was pointed out that, although the bone is developed directly from the primitive mesenchyme, precartilaginous (and later cartilaginous) elements develop at the sternal and acromial ends shortly before these regions are ossified. Cartilage growth, in some measure, is involved in this process and exostoses at either of these sites could be accompanied by shortening of the bone.

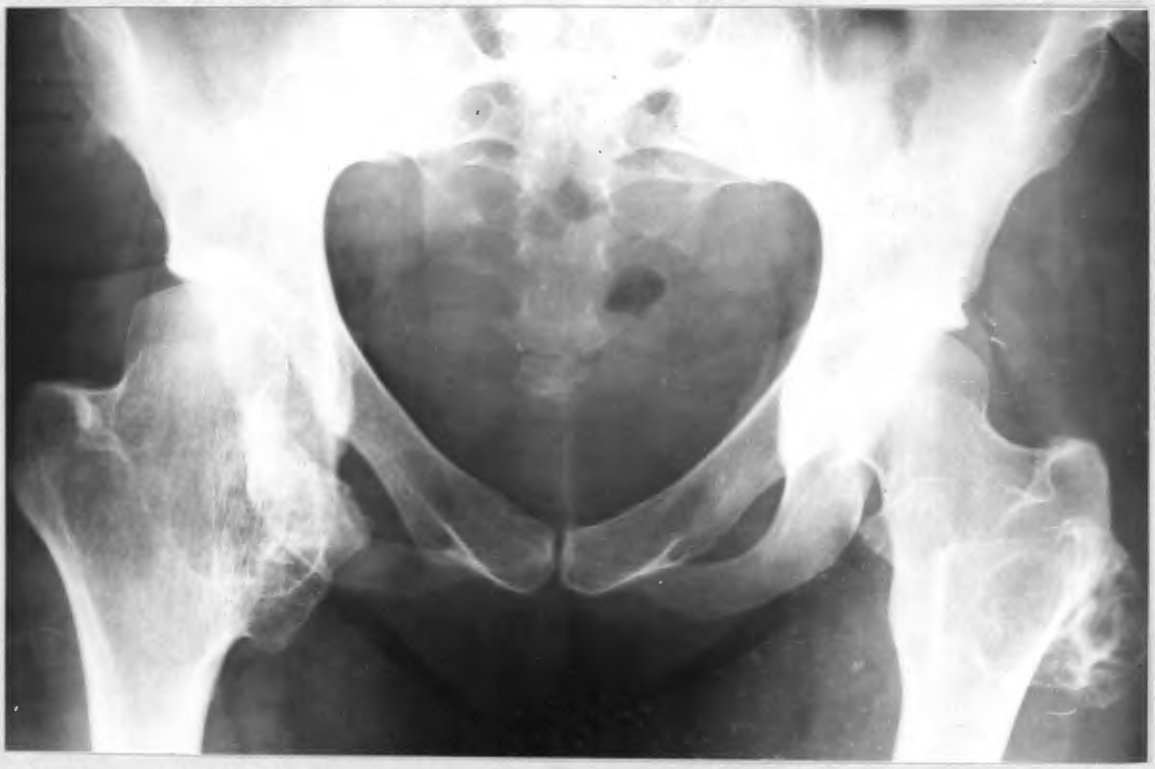

FIG. 55

Radiograph showing marked coxa valga of the right femoral neck. On the left side, where an exostosis arises from the greater trochanter, no severe deformity exists.

Coxa valga - The inability to measure accurately the angle of the femoral neck on the routine radiographs without knowing the angle of anteversion and the degree of internal or external rotation of the limb, made it impossible to assess the true incidence of coxa valga in diaphysial aclasis. Nevertheless, cases as obvious as the one illustrated in Figure 55 leave no doubt whatever about the existence of this deformity and its relationship to exostoses of the femoral neck. On the left side, where an equally large exostosis arises from the base of the greater trochanter, there is no coxa valga, an observation that was confirmed in many cases. It suggests that the deformity is due to interference with the normal growth of the femoral neck. In fact, there is not only a coxa valga but the neck, in these cases, is also abnormally short.

Short stature - Some of the earliest descriptions of multiple exostosis comment on the fact that these patients tend to be shorter than normal (134). This is a general impression which has not been substantiated by detailed anthropometric studies in large series.

The present group of patients were measured for total height, span, symphysial height and length of individual long bones.

The height distribution of these patients is shown in Figures 56 and 57.

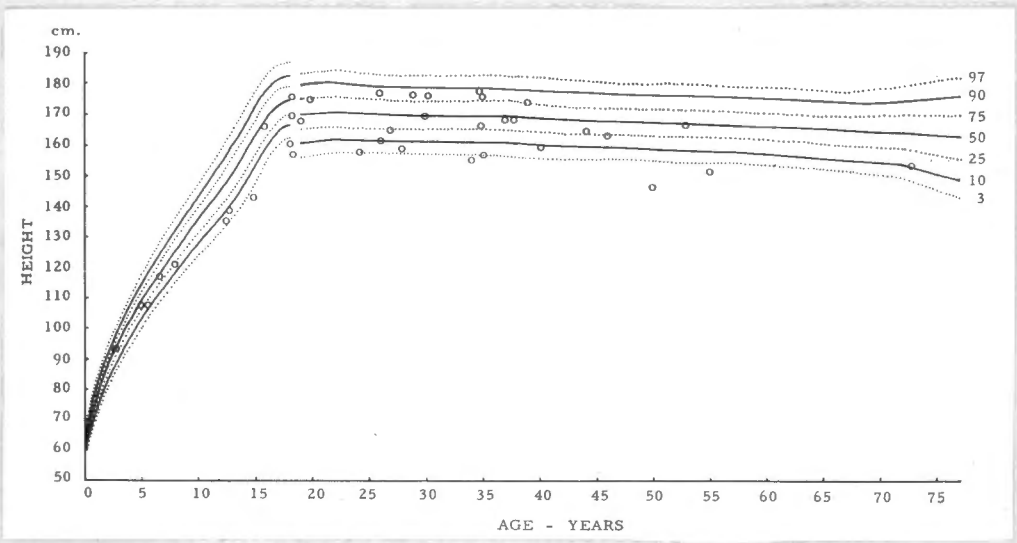

FIG. 56

The height distribution in males with diaphysial aclasis. The standard curves are derived from Tanner (1958) and Kemsley (1950). The figures on the right show the 3rd, 10th, 25th, 50th, 75th, 90th and 97th percentiles.

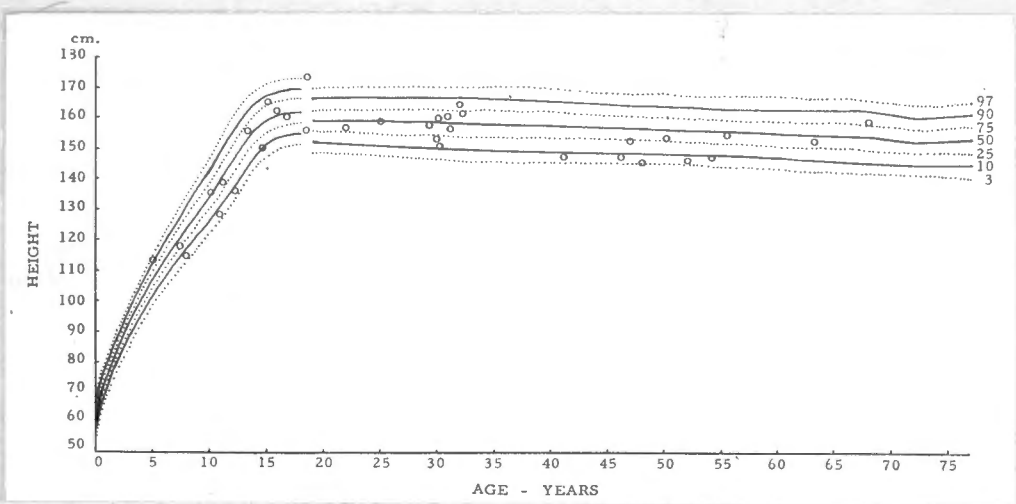

FIG. 57

The height distribution in females with diaphysial aclasis. The standard curves are derived from Tanner (1958) and Kemsley (1950). Percentiles indicated as in Figure 56 .

The standards used were derived from two sources. Up to the age of 18 Tanner's standards (137) are the most reliable, and a corresponding series of "healthy" children and adolescents attending the hospital as out-patients were found to be evenly distributed along these curves. For the adults Kemsley's standards (85) have been chosen as the most reliable and representative of the studies on British people. It is likely that the present population is slightly taller than is reflected in these standards, obtained before 1943. A series of "healthy" out-patients corresponding in age and sex to the patients with diaphysial aclasis was also measured, and compared with Kemsley's standards they all tend to be slightly taller. The fiftieth percentile in this group falls almost exactly on the seventy-fifth percentile of Kemsley's series. The values shown in Figures 56 and 57 are therefore, if anything, even lower than they seem compared to the normal.

There are several points worthy of comment in these figures. (1) The diminution in height, though undoubtedly evident, is not on the whole great. Only seven patients fell below the third percentile and can be regarded as highly abnormal. (2) The shortness of stature becomes more evident as the end of the growth period is reached. Thus, before puberty there is hardly any deviation from the normal, but from then onwards growth is clearly retarded by comparison with the normal. (3) Males, on the whole, are more severely retarded than females. This could be explained by the fact that girls reach the end of the growth period earlier than boys and the effects of diaphysial aclasis on growth continue for a considerably longer period in the latter.

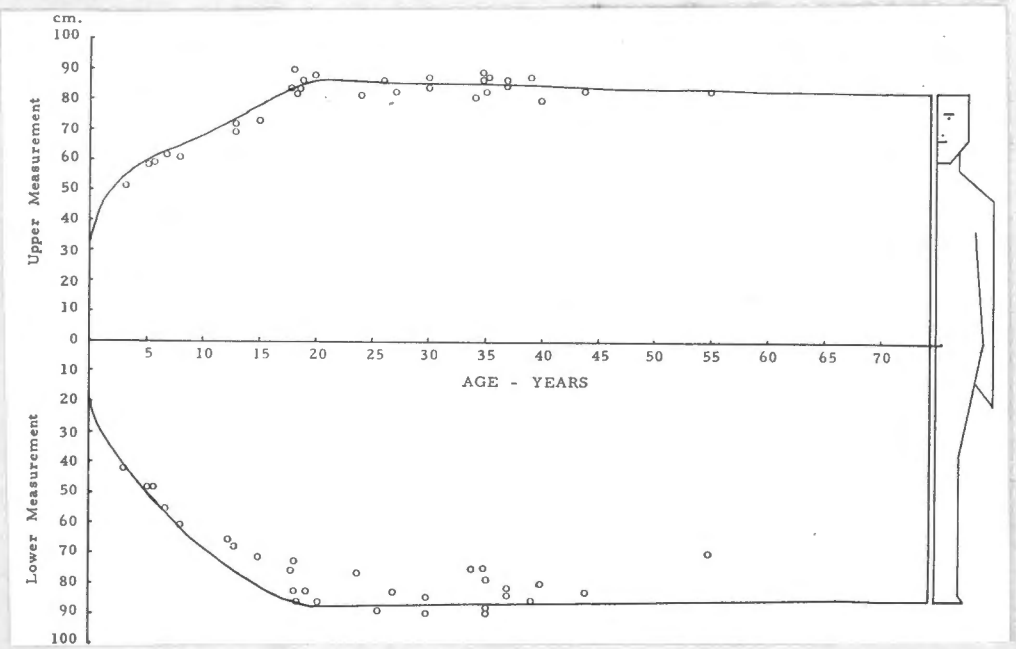

FIG. 58

Comparison of upper and lower measurements in males with diaphysial aclasis. Standards derived from Engelbach (1932).

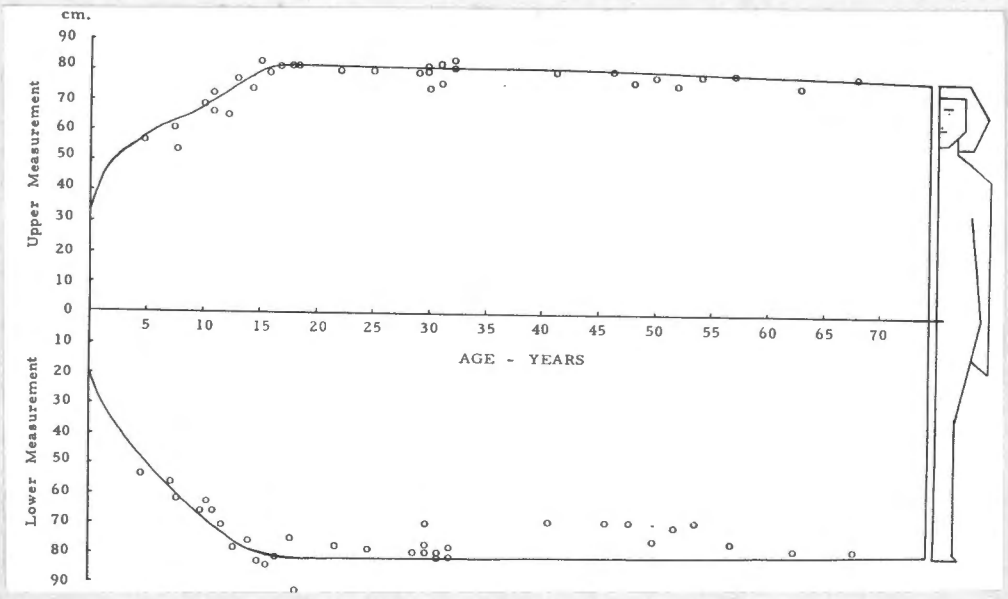

FIG. 59

Comparison of upper and lower measurements in females with diaphysial aclasis. Standards derived from Engelbach (1932).

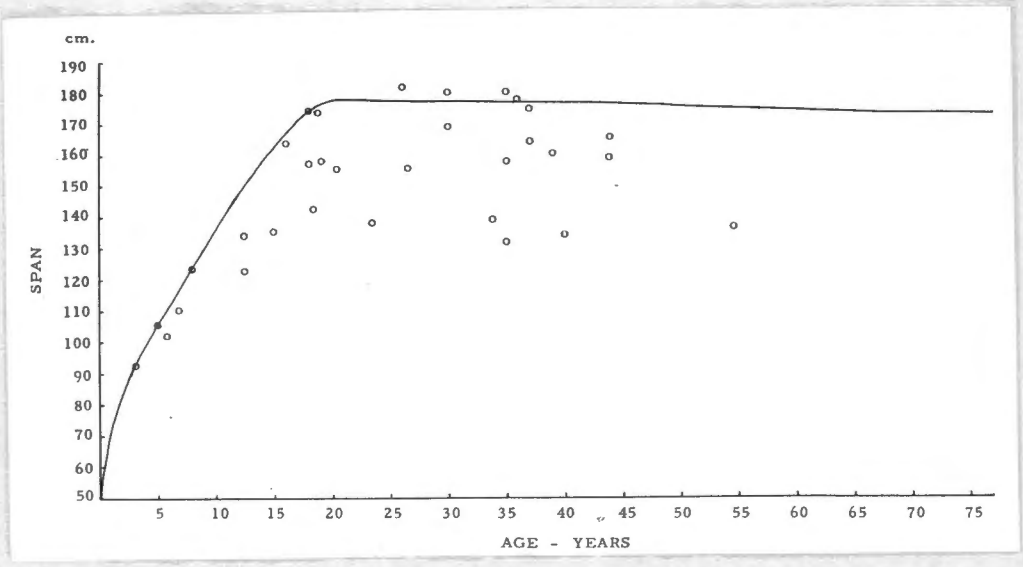

FIG. 60

Measurement of the span in males with diaphysial aclasis. The standards are derived from Engelbach (1932).

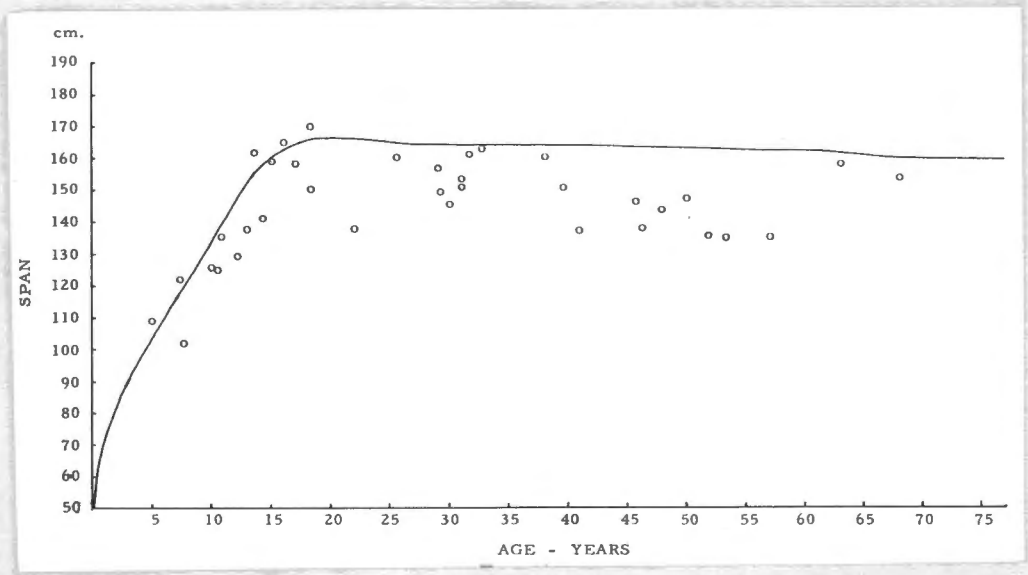

FIG. 61

Measurement of the span in females with diaphysial aclasis. The standards are derived from Engelbach (1932).

As might be expected, this diminution in stature is almost entirely due to shortness of the lower limbs, the trunk being more or less normal. Figures 58 and 59 show the "upper" and "lower" measurements in these cases compared with Engelbach's standards (1932) (43). Here again the possible errors were minimised by measuring "healthy" out-patients and the mean values were found to correspond closely to Engelbach's figures, obtained before 1932 mainly on native Americans. The symphysial height is a reliable index of total lower-limb length.

The span, from finger tip to finger tip, measures not only the combined length of the long bones but also that of the hands and the pectoral girdle. These measurements are shown in Figures 60 and 61, the standards again being those of Engelbach. Retardation of growth of the tubular bones is reflected to a much greater extent here than in either the symphysial height or the total height.

There are no reliable clinical standards for comparing the length of the individual bones, but an interesting impression was gained from studying these measurements. The degree of shortening in the long bones tends to be progressively more and more severe in the following order: the femur least of all, then tibia, humerus, radius, fibula and the ulna most severely of all. This is exactly in keeping with the suggestion

made previously that the degree of shortening is related to the cross-sectional area of the epiphysial plates of the bones affected, the narrowest bones being shortened the most and the widest the least. It has already been shown (Chapter XV) that the occurrence of exostoses is related to the growth potential of the particular site. A new dimension is now introduced: if the bone end is (normally) a region of active growth and elongation and yet depends for this growth on a comparatively small epiphysial plate, the possibility of disorganisation (and hence retardation of growth) is so much the more likely.

Pathogenesis - The cause of this retardation in growth of the long bones in diaphysial aclasis cannot be separated from the cause of the disease as a whole. There is no evidence that it is due to precocious skeletal maturation or early closure of the epiphysial plates, though this belief is still quite widelyheld (Illingworth and Dick 1956) (75). Figure 62 shows that skeletal maturation in these patients is normal and the epiphyses close at the normal times, whether the bones are affected by multiple exostoses or not. Skeletal ages were estimated accoording to the criteria of Greulich and Pyle (61) (see Chapter III, Materials and Methods) and plotted against the standards derived from the Harvard series quoted by these authors. There was no significant deviation from the normal distribution.

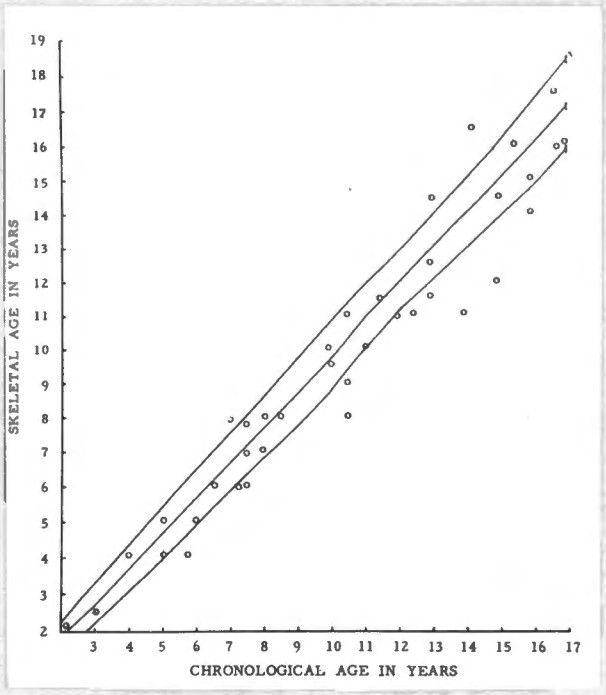

FIG. 62

Skeletal maturation in diaphysial aclasis. Standards derived from the Harvard series quoted in Greulich and Pyle (1959) and shown here as the mean and one standard deviation above and below.

The alternative theory of "squandered growth potential", though couched in less scientific terms, is much more attractive. As long ago as 1891 Bessel-Hagen suggested (12) that the bone loses in longitudinal growth what it squanders in irregular, transverse growth. This theory not only recognises the connection between the occurrence of exostoses and the retardation of growth in the affected bone, but actually regards the one thing as being dependent on the other. The appearance of these abnormal bones does suggest that the normal growth potential, which should have been directed to increasing

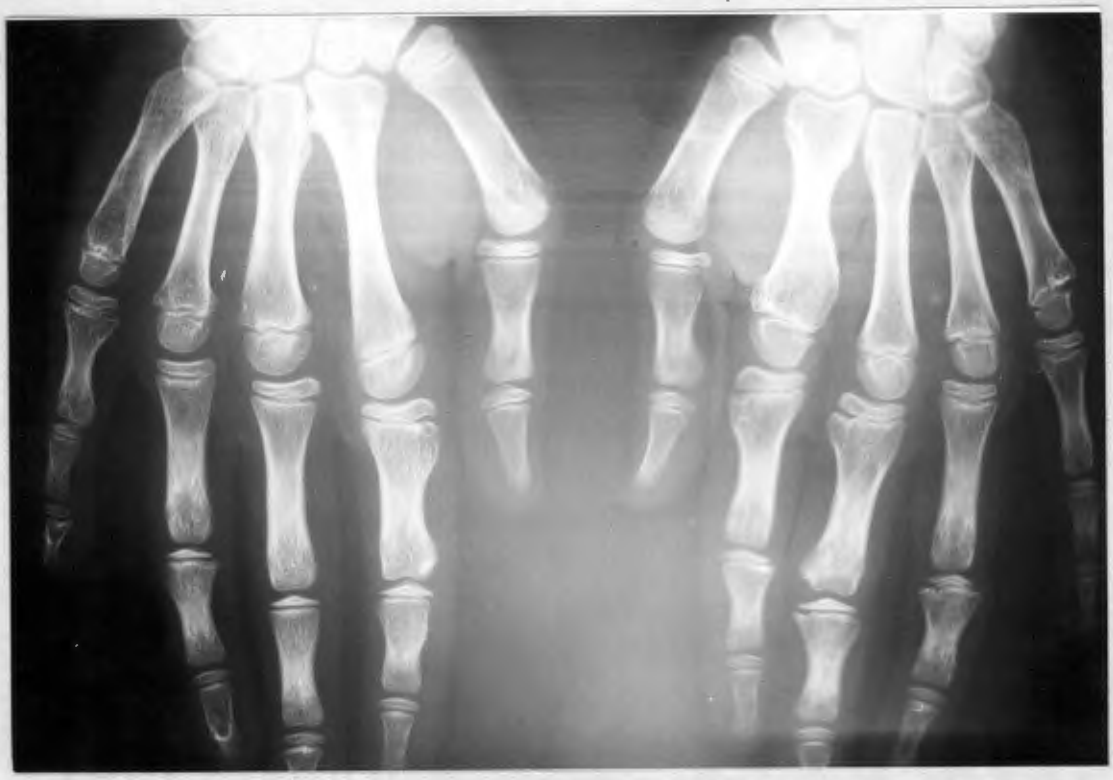

FIG. 63 (a)

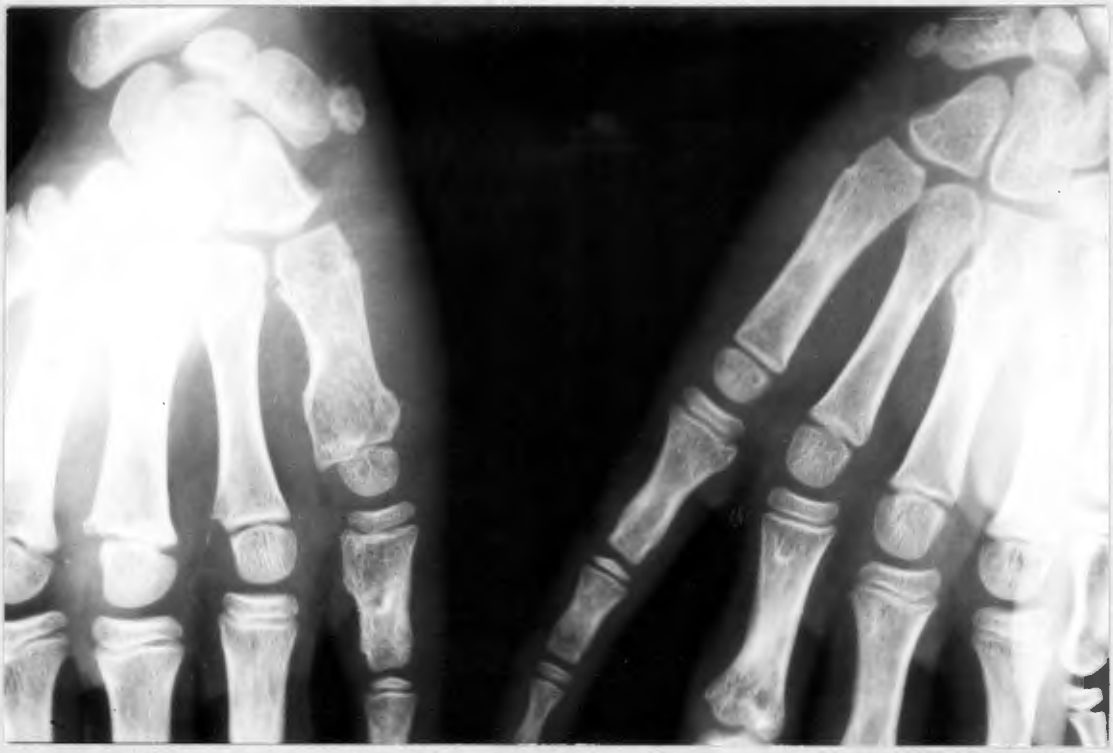

FIG. 63 (b)

Radiographs showing disproportionate shortening of affected bones as compared with unaffected opposite numbers. In Fig. 63 (a) the second metacarpal of the left hand is the bone concerned. In Fig. 63 (b) the right fifth metacarpal and the proximal phalanx of the fifth finger are broader and shorter than the unaffected, corresponding bones of the left hand.

the length of the bone, has been squandered on the formation of abnormally broad metaphyses and multiple exostoses. Certain it is that a bone which is markedly broadened in the metaphysial region, possibly with numerous exostoses as well, is invariably shorter than an unaffected opposite number. Three examples of this phenomenon are shown in Figure 63. Compare,also, the right and left ulna in Figure 51. Whether the degree of shortening is exactly proportionate to the overall thickening of the metaphysial region is impossible to determine unless the entire skeletal system is available for morbid anatomical studies at various ages during the period of growth.

(b) ADAPTATIONS OF BONE GROWTH DUE TO PRESSURE BY ADJACENT EXOSTOSES.

Certain abnormalities of bone growth are induced simply by prolonged pressure from adjacent exostoses (Fig. 50). By the process of osteoclastic resorption and bone modelling the growing bone accommodates itself to the obtrusive exostosis in the characteristic way. (Fig. 64). This occursquite frequently in the radius and ulna, the tibia and fibula and in adjacent ribs, but may also be seen in almost any situation where a large exostosis abuts on a neighbouring bone, or even on the very bone from which it arises.

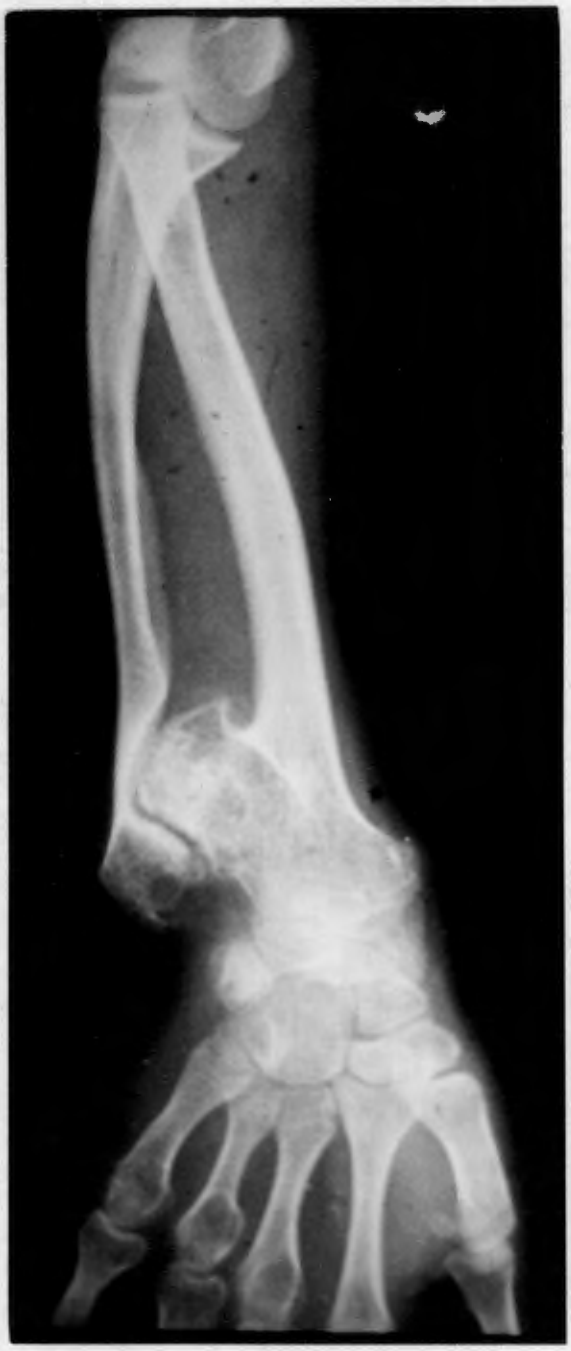

FIG. 64

Osteoclastic resorption and modelling of the ulna induced by pressure from an adjacent exostosis of the radius.

Tibio-fibular synostosis - Whereas a growing bone will mould itself in the manner described, if two adjacent exostoses abut against each other the results are quite different. If either of the two exostoses continues to grow, the one will gradually become embedded in the cartilaginous cap of the other and this may eventually go on to synostosis between the two bones (Fig. 65). This is distinctly unusual in the radius and ulna, where supination and pronation movements probably prevent such an outcome, but tibio-fibular synostosis occurred in 19 (or 25 per cent) of the 76 patients in whom complete radiographic examinations were carried out, and of these all but three were affected bilaterally. It is perhaps worth commenting that, apart from the fact that most of these patients also had valgus deformities of the ankles, function was otherwise undisturbed.

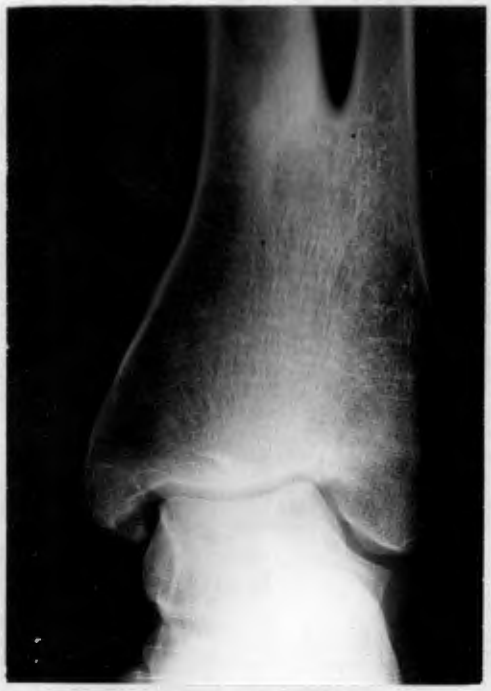

FIG. 65

Radiograph showing tibio-fibular synostosis in a patient with diaphysial aclasis.

2. MIGRATION OF EXOSTOSES.

The exostoses, once formed, may be thought to retain their relationship to each other, at least at their attachment to the diaphysial shaft. In studying the radiographs of children with multiple exostoses one is often struck by the fact that two easily identifiable exostoses - one at the proximal and one at the distal end of the bone - appear to move farther and farther apart over the years. Figure 66 shows two successive radiographs,

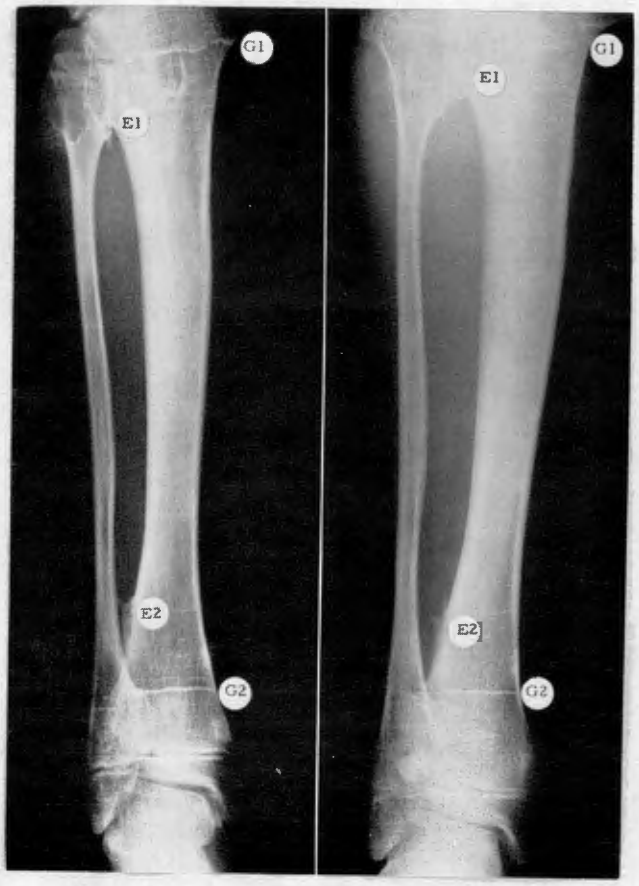

FIG. 66

Radiographs of the right tibia and fibula at fourteen years and sixteen years. The exostoses E1 and E2 have moved farther apart over the period of two years, while the lines G1 and G2 have remained unchanged.

the one taken at the age of 14 and the other at the age of 16. In the earlier radiograph the exostoses E1 and E2 are 15.1 centimetres apart. In the later radiograph they are 16.8 centimetres apart. Only one other reference to this phenomenon has been discovered in a careful search of the literature (Lacroix 1950) (89). Yet it is the rule rather than the exception for this to occur and it can be demonstrated in almost every case provided appropriate radiographs are taken at successive ages during the period of growth.

The fortuitous co-existence of "Harris's lines" in some of these cases has allowed a comparison with bone growth as a whole. Figure 66 shows that, whereas the distance between the exostoses increases, the distance between the lines G1 and G2 remains the same over the years. In other words, diaphysial length has remained unchanged, while the exostoses have moved farther and farther apart. Logically, there can be only one cause for this phenomenon - namely, progressive osteoclastic resorption on the diaphysial side and simultanoues osteoblastic new bone formation on the epiphysial side of each exostosis. Figures 67, a and 67,b show the histological features of one such case. This exostosis had demonstrably altered its relationship to a nearby Harris's line by no less than 1.5 centimetres over the space of five years. When ultimately excised (on

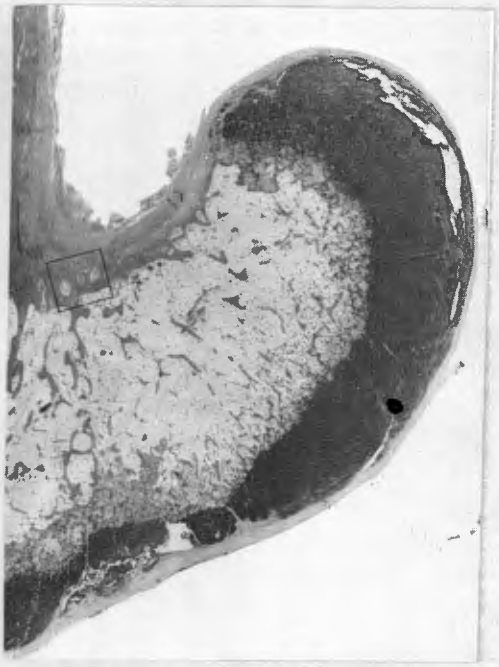

FIG. 67, a

Photomicrograph of an exostosis showing the region where osteoclastic resorption and new bone formation have been demonstrated.

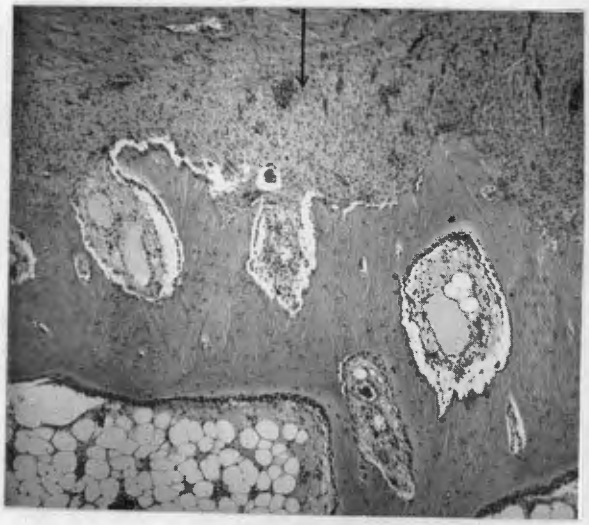

FIG. 67, b

Photomicrograph of the area marked out in Fig. 67, a. Osteoblasts are massed along the advancing edges of the bone trabeculae while the trailing edges are ragged with numerous Howship's lacunae. (The arrow shows the direction in which the exostosis is migrating).

account of continuous pain) a small piece of the adjacent cortex was taken as well (Fig. 67,a). The base of the exostosis shows numerous osteoclasts in their lacunae along the margin facing towards the mid-shaft, and the bony trabeculae are being actively replaced by rows of osteoblasts massed along the opposite margins. It is not known, with certainty, what stimulates this process. However, it seems unnecessary to invoke any special mechanism to account for this phenomenon. It appears to be no different from the normal process of osteoclastic and osteoblastic "modelling" which occurs at the fluted ends of the long bones. And, incidentally, it establishes the fact that "modelling" continues quite actively in these abnormal bones, a fact which will be referred to again in the next chapter.

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3. DISAPPEARING EXOSTOSES.

An early reference to disappearing exostoses can be found in John Hunter's Lectures of 1786, published in 1835. Writing about the treatment of the condition he says: "It is hardly ever to be cured by medicines either external or internal, but as it is sometimes spontaneously removed we should endeavour to promote the absorption of it by rousing up this power."

About one-third of the adult patients say that one or more of the bony lumps which they had in childhood have gradually disappeared over the years. This raises an important question and might have a bearing on treatment. These statements were therefore investigated with particular care, and were substantiated in a surprising number of cases.

Figure 68 shows a typical example of disappearing exostoses. The exostosis at the base of the proximal phalanx of the left middle finger has disappeared completely by the age of 10; the smaller exostosis which shows at this age at the distal end of the proximal phalanx of the right middle finger has likewise disappeared by the age of 13½.

The explanation for this is probably quite simple. The overall diameter of the phalangeal shaft plus the exostosis in each case remains unchanged over the years. Clearly the exostosis must have ceased growing while the phalanx enlarged in the normal way, increasing its diameter

by appositional growth until the overall dimensions obscured the once prominent exostotic projection.

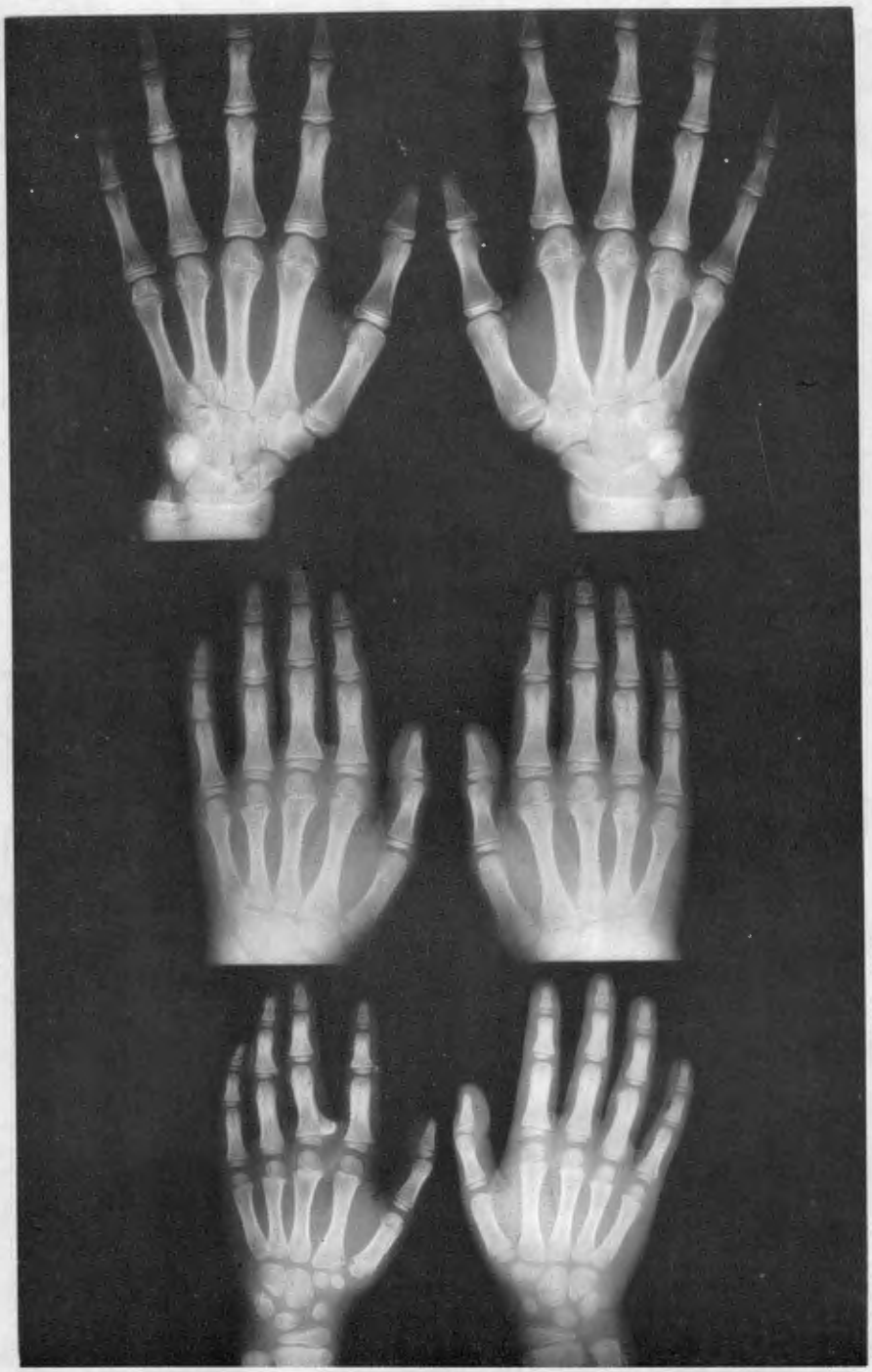


FIG. 68

Successive radiographs of a child's hands showing the dis-appearance of exostoses between the ages of five and thirteen and a half years.

CHAPTER XVII.

THE PATHOGENESIS OF THE LESIONS IN MULTIPLE EXOSTOSIS.

The preceding four chapters have been devoted to an elucidation of the abnormality which we recognise as hereditary multiple exostosis. Certain concepts have been formulated regarding the genetic characteristics of the condition and its mode of expression in the phenotype. We have learnt that it is usually transmitted by an autosomal dominant gene which expresses itself in affected individuals as a disorder of endochondral growth and ossification; that the evolution of detectable bone lesions is determined by the normal manner of growth at the affected site; and that the associated skeletal deformities are due to diminished growth of the affected bones. The links that connect these three statements are yet to be discovered; together they would describe the precise microscopic deviation from the normal pattern of growth.

The less that is known of a disease the more multitudinous are the theories explaining it, and hereditary multiple exostosis is no exception. Certain hypotheses, derived from experiment and direct observation, will be considered below. Thereafter, the more likely theoretical explanations will be analysed in the light of the findings of this study.

ABNORMAL GROWTH OF THE EPIPHYSIAL PLATE.

Abnormalities following trauma to the epiphysial plate.

Trauma to the epiphysial plates of growing animals may produce a profound disturbance, and even total arrest, of growth. This is the basis for the operation of epiphysiodesis to bring about the cessation of growth at a particular site. However, it has also served as an experimental tool in the study of bone growth.

Many different forms of the same experiment have been devised. Essentially this consists of either destroying some part of the epiphysial plate or bridging the disc with nails, screws or bone grafts. One such study, on dogs, was reported by Campbell, Grisolia and Zanconato (1959) (19). Ford and Key (1956) (51) studied the effects of damaging the central and peripheral parts of the plate in growing rabbits and noted, in passing, that osteocartilaginous exostoses resulted from displacement of fragments of epiphysial cartilage from the periphery of the disc. This, together with a retardation of growth, appears to combine the two essential elements encountered in diaphysial aclasis. However, in all these experiments, retardation of growth was associated with extensive changes in the epiphysial cartilage itself, resulting in its early obliteration with fusion of the epiphysis and metaphysis. The situation encountered in diaphysial aclasis, where diminished bone growth is associated with a normal period of epiphysial activity and normal closure of the epiphysial plates at the end of growth, has not been reproduced in any of these experiments.

Exostoses following irradiation.

The development of cartilage-capped exostoses after radiation therapy in children has been reported by a number of people (22; 47; 109; 133). In some of these cases there is also a marked retardation of growth. Moreover, the effects of ionising radiations have been known to produce multiple exostoses, as in the three cases reported by Spiess (1957) (133) ; these patients had received Thorium-X, a bone seeking radio isotope.

Spiess' observations are of particular importance and lend considerable support to some of the conclusions presented in this thesis. In each of his three patients the period of epiphysial damage during exposure to Thorium-X was marked by metaphysial "calcification bands" and each of the cartilage-capped exostoses was related precisely to one such band. Autoradiographic examination of these areas showed that the isotope was strongly active in these bands, thus presenting a neat correlation between irradiation, epiphysial damage and exostotic growth of cartilage.

Similar lesions have been produced experimentally in rabbits after exposure of the epiphyses to radiation (5,000 - 20,000 r.) (92,a) and it has been suggested that they are due to arrested development of the peripheral cells of the cartilage plate and their failure to differentiate normally into the cells of the proliferative layer of the periosteum.

Unlike other types of experimental exostosis,

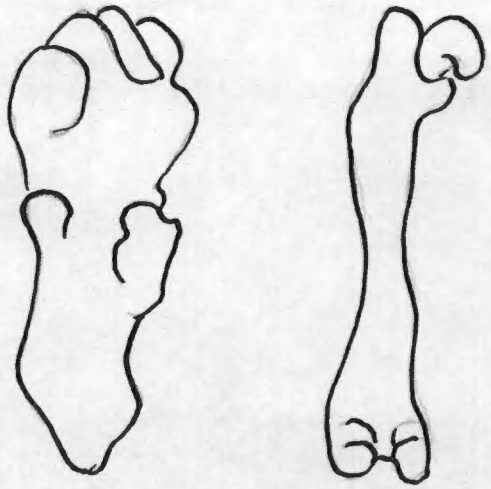
these lesions are associated with a normal period of epiphysial growth, a further similarity to diaphysial aclasis.

MULTIPLE EXOSTOSES IN EXPERIMENTAL LATHYRISM.

Lathyrism has been produced experimentally in rats by feeding them with a diet of sweetpea seeds (Lathyrus odoratus). The toxic agent, beta-aminopropionitrile, interferes with normal connective tissue metabolism (possibly inhibiting the synthesis of sulphated mucopolysaccharides), causing widespread abnormalities of the musculo-skeletal system. These have been well described by Ponseti and Shepard (118), Yeager and Hamre (153) and Dasler (32).

The characteristic bony lesions produced in young growing rats are weakening and even disruption of the epiphysio-diaphysial junctions, loosening of the periosteum at the tendinous and ligamentous attachments, and marked thickening of the long bones with multiple exostoses prominent at the sites of muscle attachment (Fig.69).

Superficially these lesions resemble diaphysial aclasis, but there are strong points of difference that place them quite outside the category of a developmental abnormality. There is no diminution in the length of the affected bones (Fig. 69), and indeed the lesions have been produced in adult rats as well. (153). They are not related to the epiphysial discs but occur along the shaft of the bone at the



(a) (b)

FIG. 69

(a) Posterior aspect of the femur of a rat after a diet of fifty per cent sweat peas for twenty-one days; and (b) normal pair-fed control. (After Dasler, 1957).

points of muscle attachment. This is an important feature of the disease. Hamre and Yeager (1958) (153) have described the development of these lesions in the subperiosteal connective tissue and have shown that they arise upon the surface of the cortex by membranous ossification in the proliferative layer of the periosteum and do not develop any cartilaginous element.

ACID MUCOPOLYSACCHARIDE EXCRETION IN DIAPHYSIAL ACLASIS.

In 1960 Lorincz reported that the urinary excretion of acid mucopolysaccharides (AMPS) was greatly increased in multiple exostosis and suggested that this was due to a disorder of connective tissue AMPS metabolism. (102). As the same observation has been made in Hurler's syndrome (138) Lorincz's suggestion was regarded as significant and important. The investigation was therefore repeated in 20 subjects of the present series: 13 affected patients and seven unaffected sibs from Families Number 5, 9 and 38 (see Appendix I). Their ages ranged from 3½ to 64 years.

The method used for estimating urinary AMPS was that described by Di Ferrante and Rich (1956) (33). Each value was expressed as a ratio of AMPS (glucuronic acid) to creatinine in any given sample of urine; these were plotted against the normal standards of Teller, Burke, Rosevear and McKenzie (see Material and Methods, Chapter III). The results are shown in Figure 70.

It is seen here that the values in most of the unaffected sibs fell slightly below the mean. Among the affected patients those under the age of 16 years had values well above the mean (with a single exception) but still within the 95 per cent probability range. In the affected adults AMPS excretion was not raised at all.

The finding of a somewhat raised AMPS excretion in children with multiple exostosis can be explained by the greatly increased bulk of cartilage, which is the main

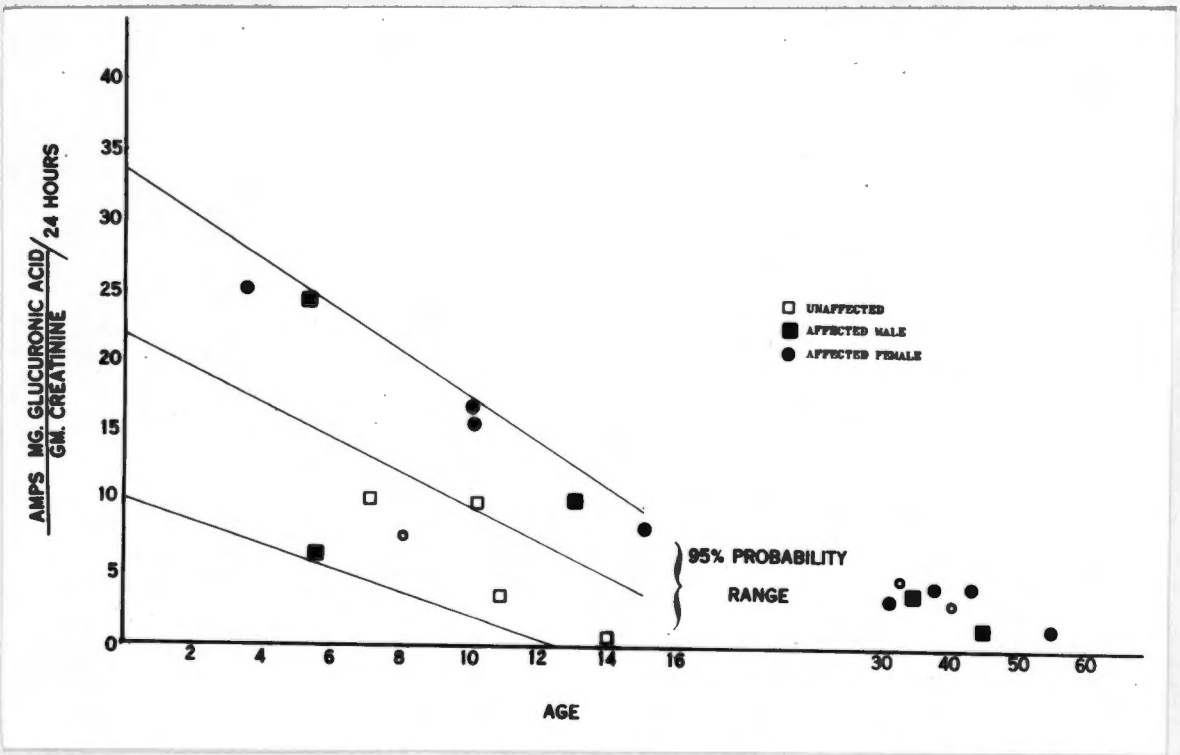


FIG. 70

Urinary acid mucopolysaccharide levels in thirteen patients with multiple exostosis, and seven unaffedted sibs. The standards used are derived from Teller, Burke, Rosevear and McKenzie (1962).

source of AMPS. The normal values in adult patients (whose lesions are likely to contain very little cartilage) support this view. Thus there were no grounds, on the present evidence, for postulating a specific metabolic abnormality.

With these observations we reach the present boundary between verifiable fact and rational deduction.

Of the many theories that have been advanced to explain the basic defect of growth in diaphysial aclasis only four warrant serious attention, those of Müller (1941), Keith (1920), Murk Jansen (1928), and Langenskiöld (1947).

(1.) Müller (1914) (106) observed, in the endochondral bones of a patient with multiple exostosis, small collections of cartilage cells arising from the proliferative layer of the periosteum. He suggested that these developed into exostoses and were due to a basic abnormality of the periosteum.

Müller's observations have been confirmed by others (Scherer, 1928; Jaffe, 1943), and were recalled in some cases of the present series as well (see Chapter VIII). However, there are serious objections to his theory of the pathogenesis of multiple exostosis. All the patients so far described as showing this phenomenon have been adults and it is not known whether it occurs in areas that later develop exostoses. Furthermore, this could not account for the retardation of bone growth and the associated deformities which have been described, nor would it explain the distribution of the lesions in relation to the growth potential of the particular site, as defined in Chapter XV.

(2.) Keith (1920) (83) on studying the radiographs of several cases of multiple exostosis, noted that the cortical density invariably stopped short at the metaphysial deformity (an observation which may be verified in several of the radiographs reproduced here). He believed that a sleeve of cortical bone extending up to the epiphysial plate was

required to confine the growing cartilage to its normal dimensions and prevent undue transverse growth; the absence of this cortical cuff would leave the epiphysial plate "exposed on the surface of the shaft and ..... free to give rise to irregular outgrowths or exostoses". He suggested that this was the case in multiple exostosis and attributed the abnormality to a lack of co-ordination between endochondral ossification and longitudinal growth at the epiphysial plate and subperiosteal new bone formation at the periphery of the plate. The most vital aspect of Keith's theory is that this is an abnormality of epiphysial growth and modelling, which could account for the associated skeletal deformities.

The existence of such a sleeve or sheath of bone was discussed in detail in Chapter XIII where it was concluded that, if it does occur in the form of Lacroix's "perichondrial ring of bone," it plays no part in limiting the transverse growth of the epiphysial plate but merely acts as a supporting corset for the ossifying cartilage. Its almost complete absence in some of the older subjects studied had not led to the irregularity of growth which Keith suspected.

Nevertheless the lesions which have been described do suggest a dysfunction of whatever system normally co-ordinates the parameters of cartilaginous growth, and in this sense Keith's theory has a validity which is not even approached by some of the other hypotheses.

(3.) Mürk Jansen's theory (1928) (78) would not warrant discussion were it not that this view is one of the most popular. It has the immediate appeal of simplicity : according to Jansen the broadening of the metaphysis and the associated exostoses are due to a "failure of tubulation" - that is to say, the bone which should normally be removed by the processes of modelling persists in an abnormal form. This is readily appreciated by referring to Figure 34, Chapter XIII. In the case of a stalked exostosis this defect is partial, resulting in a notch or cleft between the area of abnormal growth and the normal diaphysis - to quote Jansen, "Two diaphyses are, as it were, formed side by side."

This bears no resemblance to the observed facts, for the exostoses grow not by a deepening of the cleft between exostosis and shaft, but by the independent activity of the cartilage cap. Nor does this account for exostoses on the irregular bones which are not "tubulated", or the existence of "broad metaphyses" far in excess of the dimensions which could result from a simple failure of "tubulation". Finally, Jansen's theory fails to account for the diminution in bone length in diaphysial aclasis.

(4.) The important question of how, exactly, the epiphysial plate extends its transverse diameter during growth was examined in Chapter XIII. If it could be accepted that this occurs by a process of interstitial growth, with the

most peripheral cells being transformed into the proliferative layer of the overlying perichondrium or periosteum, then Langenskiöld's theory (1947) is the most plausible of all. He explained the development of multiple exostosis as due to a persistence of the chondrogenic property of these most peripheral cells. This concept disposes of the main objection to Keith's theory and is not incompatible with Müller's observations. Moreover, as it actively involves the proliferative zone of the epiphysial plate in the abnormality it could account for the associated retardation of bone growth.

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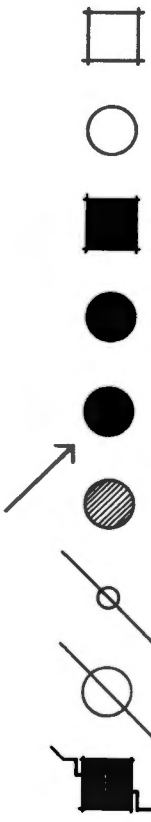
This short excursion into the realm of conjecture serves to recall those large areas of knowledge that are yet to be discovered, and thereby to define the more clearly the region which has been explored in this work. In bringing this thesis to a close the hope is expressed that some order may have been introduced into this one area, where disorder prevailed before.

APPENDIX I

PEDIGREES OF THIRTY-NINE FAMILIES WITH HEREDITARY MULTIPLE EXOSTOSIS

KEY



UNAFFECTED MALE

UNAFFECTED FEMALE

MALE WITH MULTIPLE EXOSTOSIS

FEMALE WITH MULTIPLE EXOSTOSIS

INDEX CASE

DOUBTFUL CASE

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DEATH DUE TO CHONDROSARCOMA

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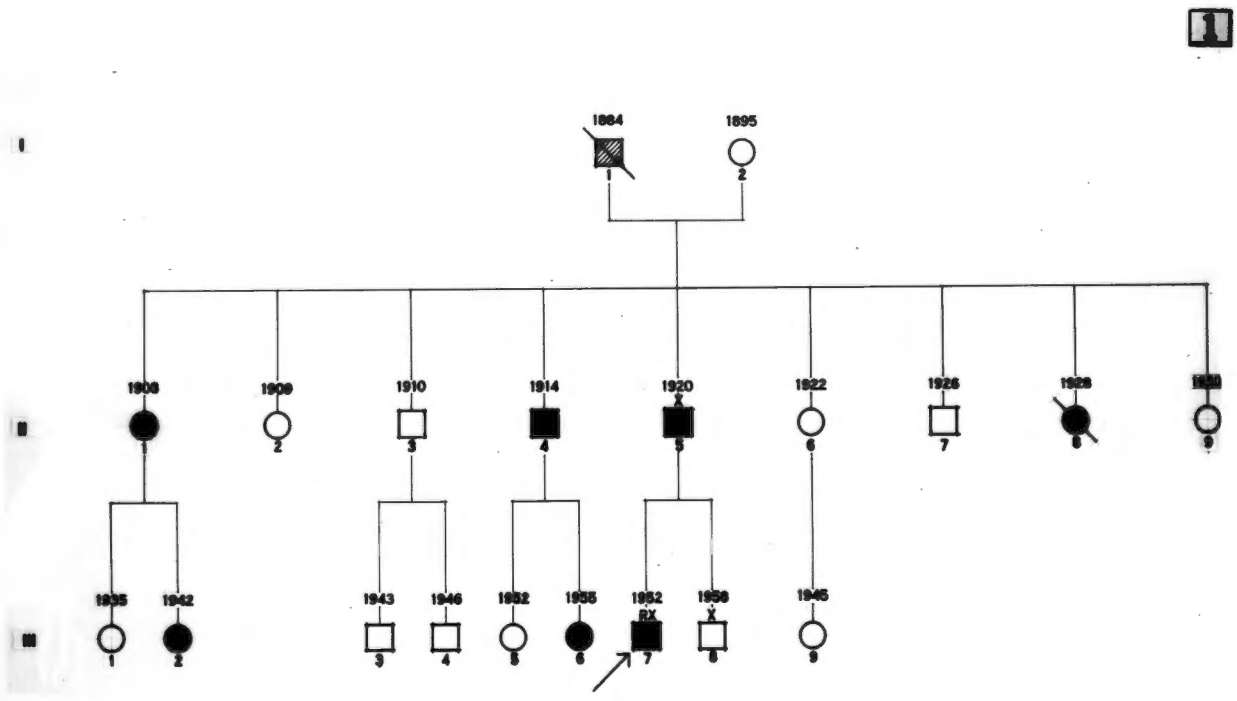
R EXAMINED RADIOLOGICALLY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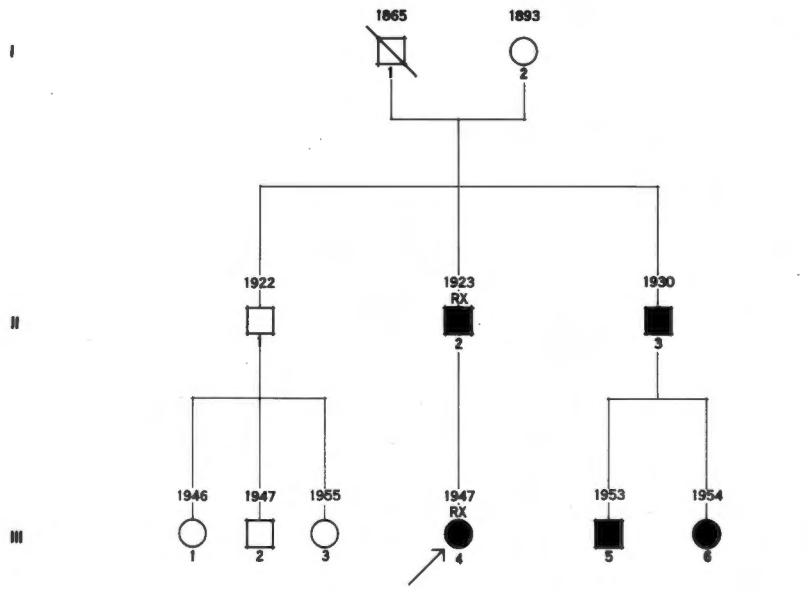
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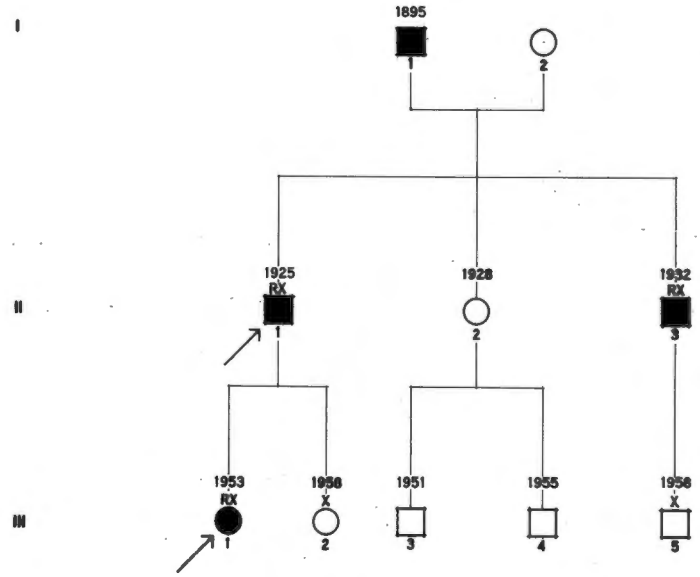
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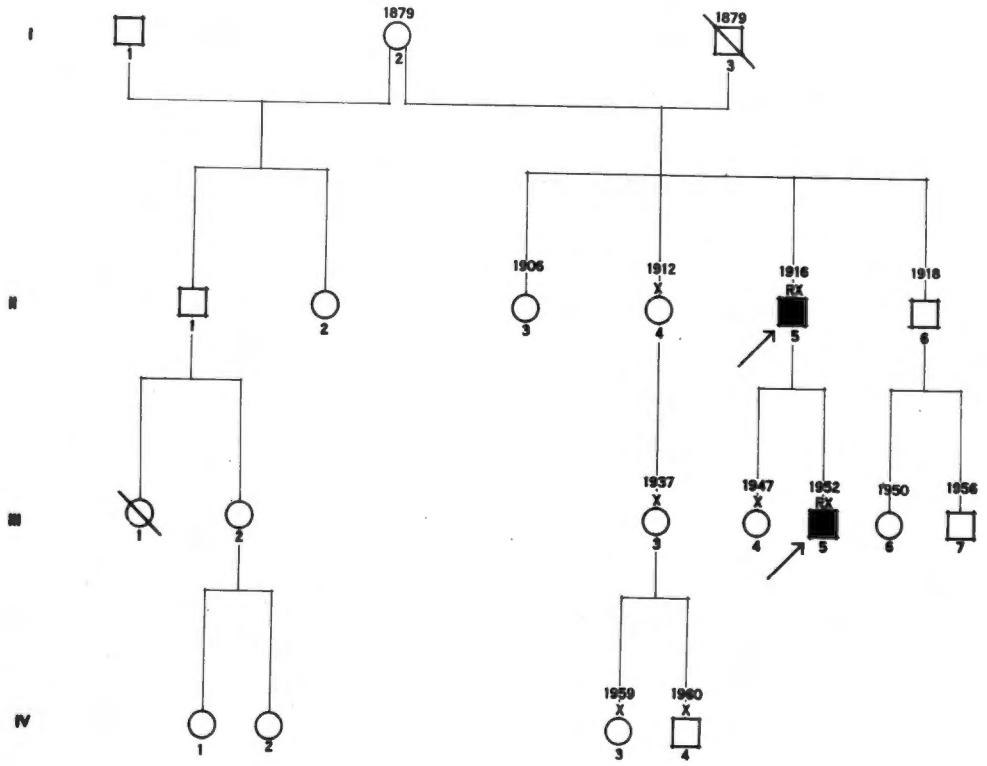
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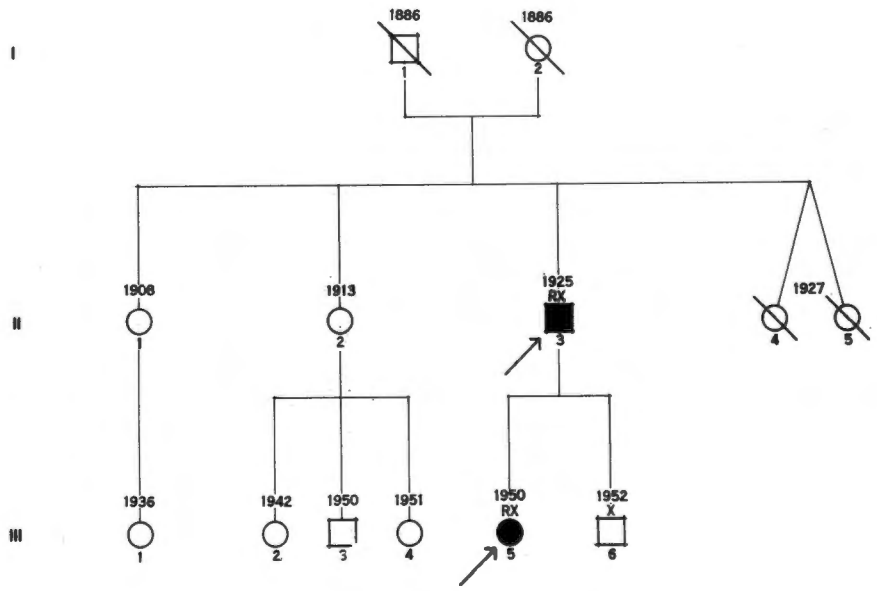
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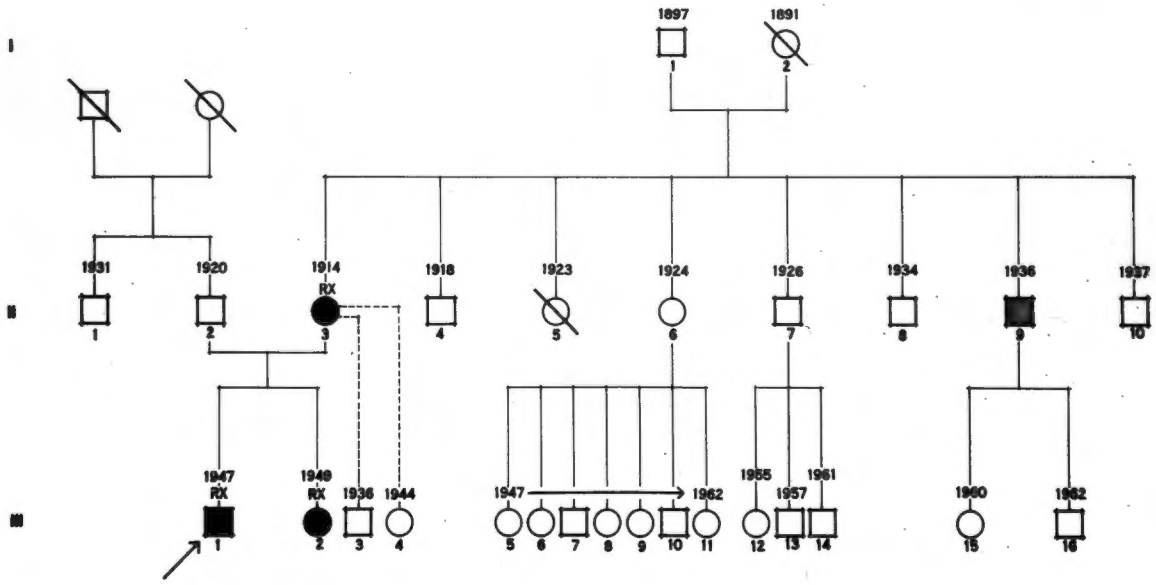
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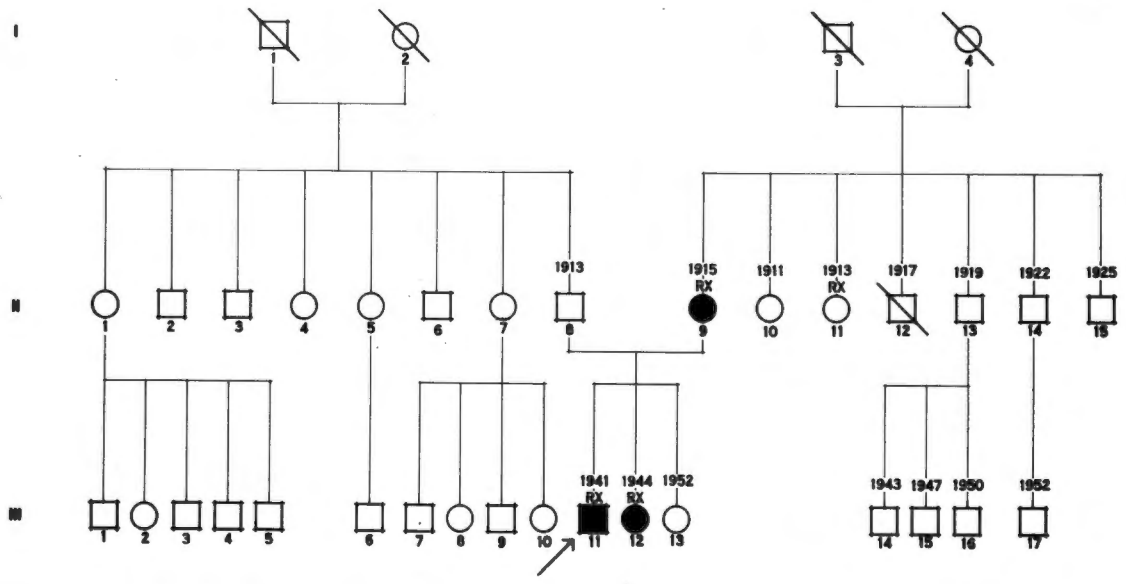
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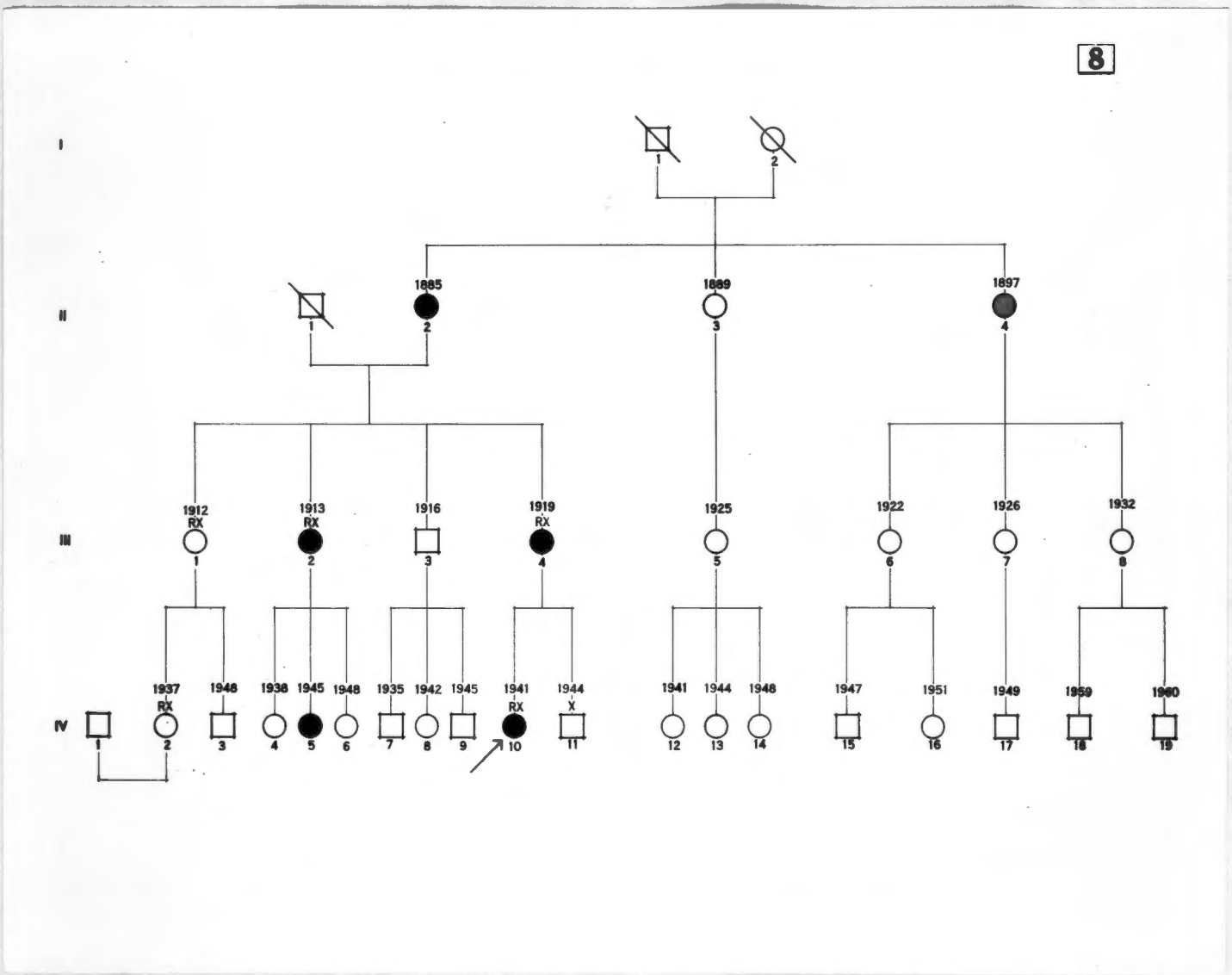
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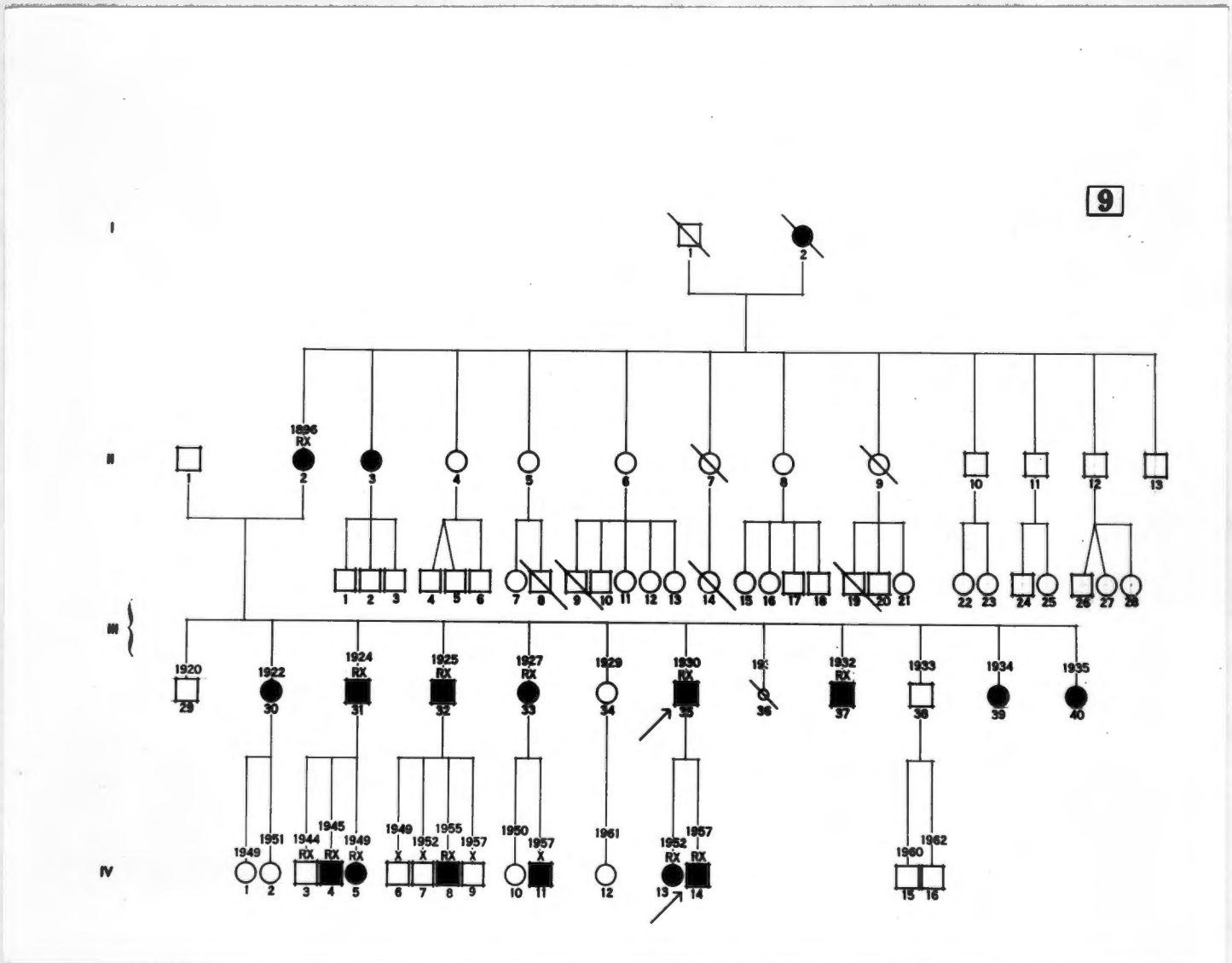
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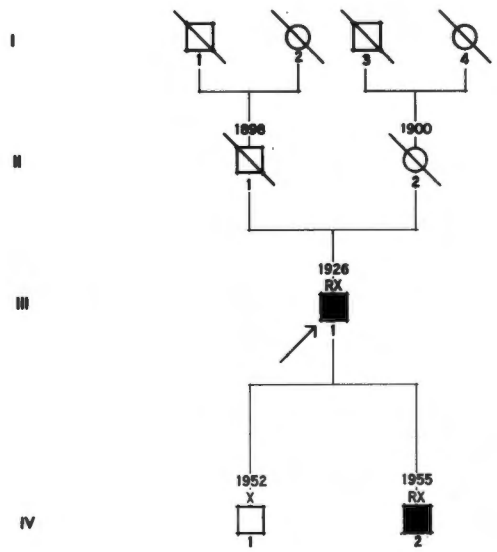

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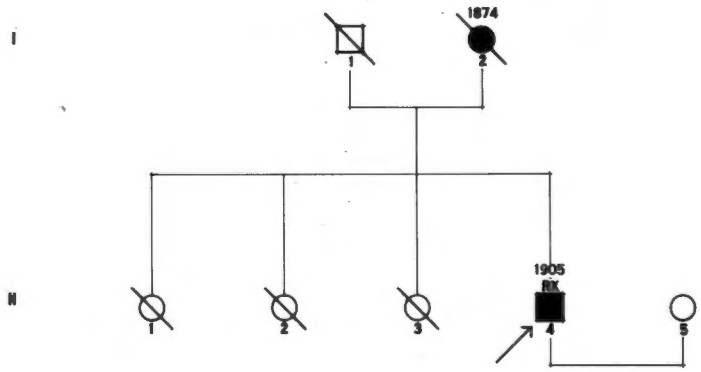

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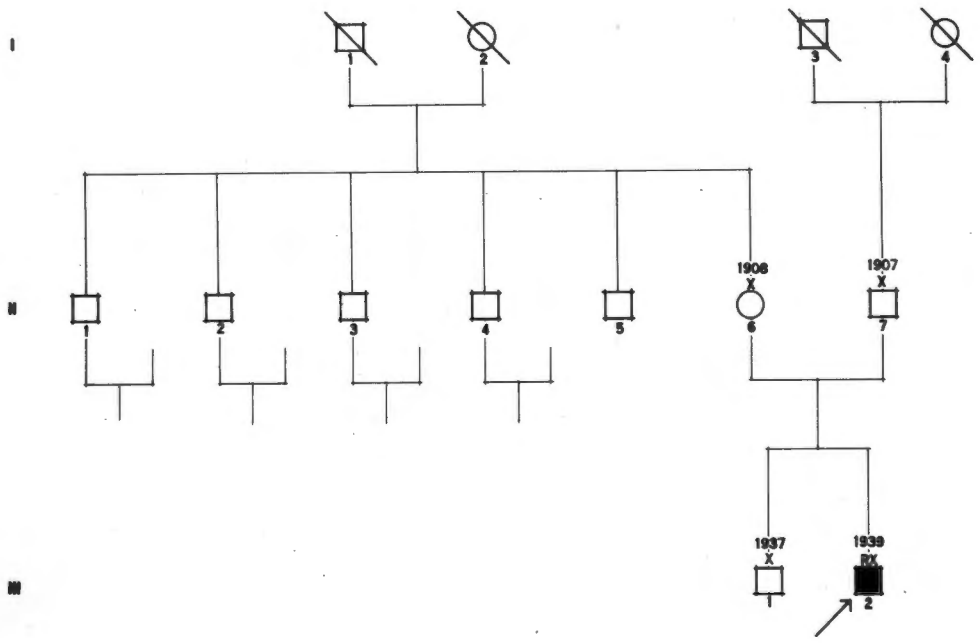

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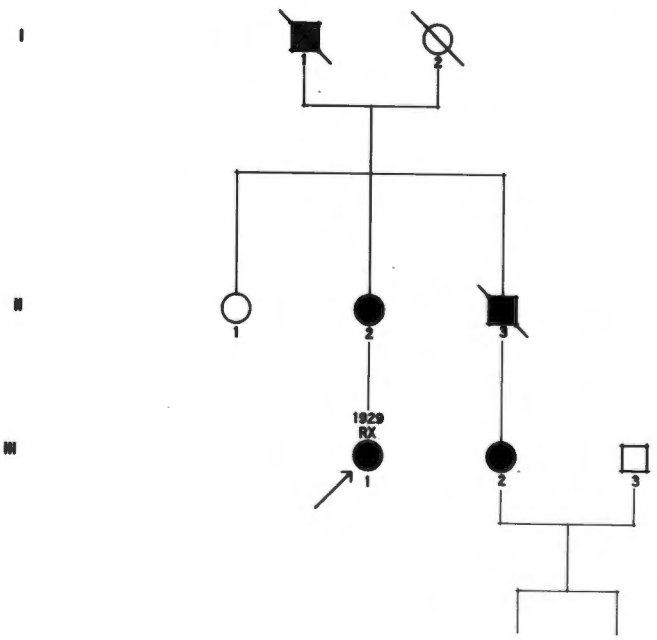

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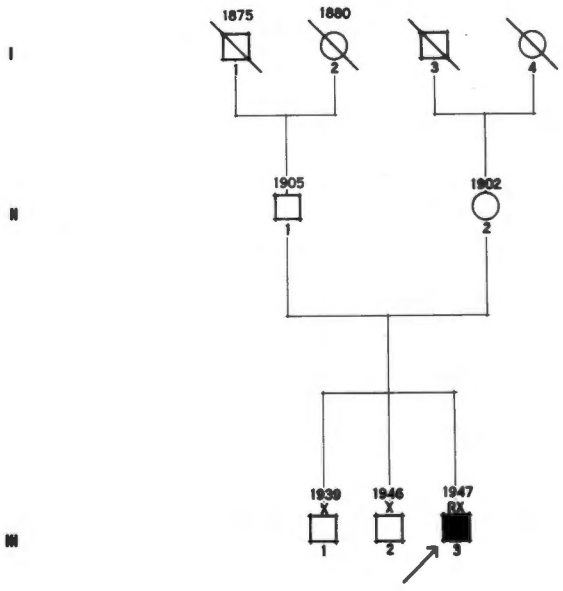

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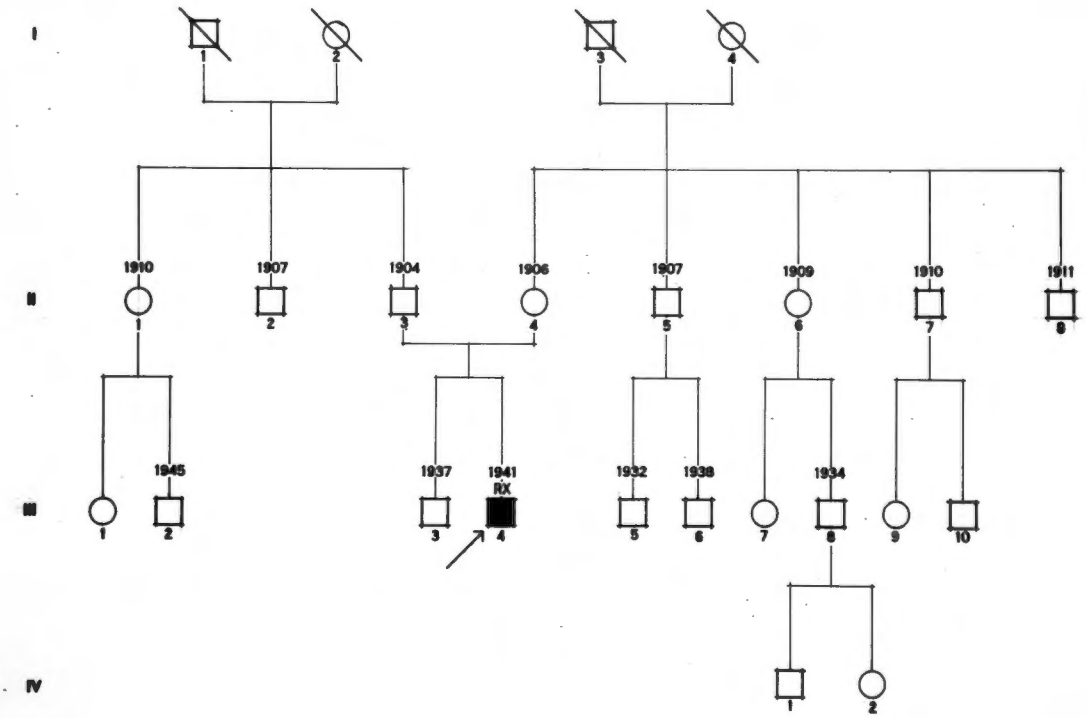
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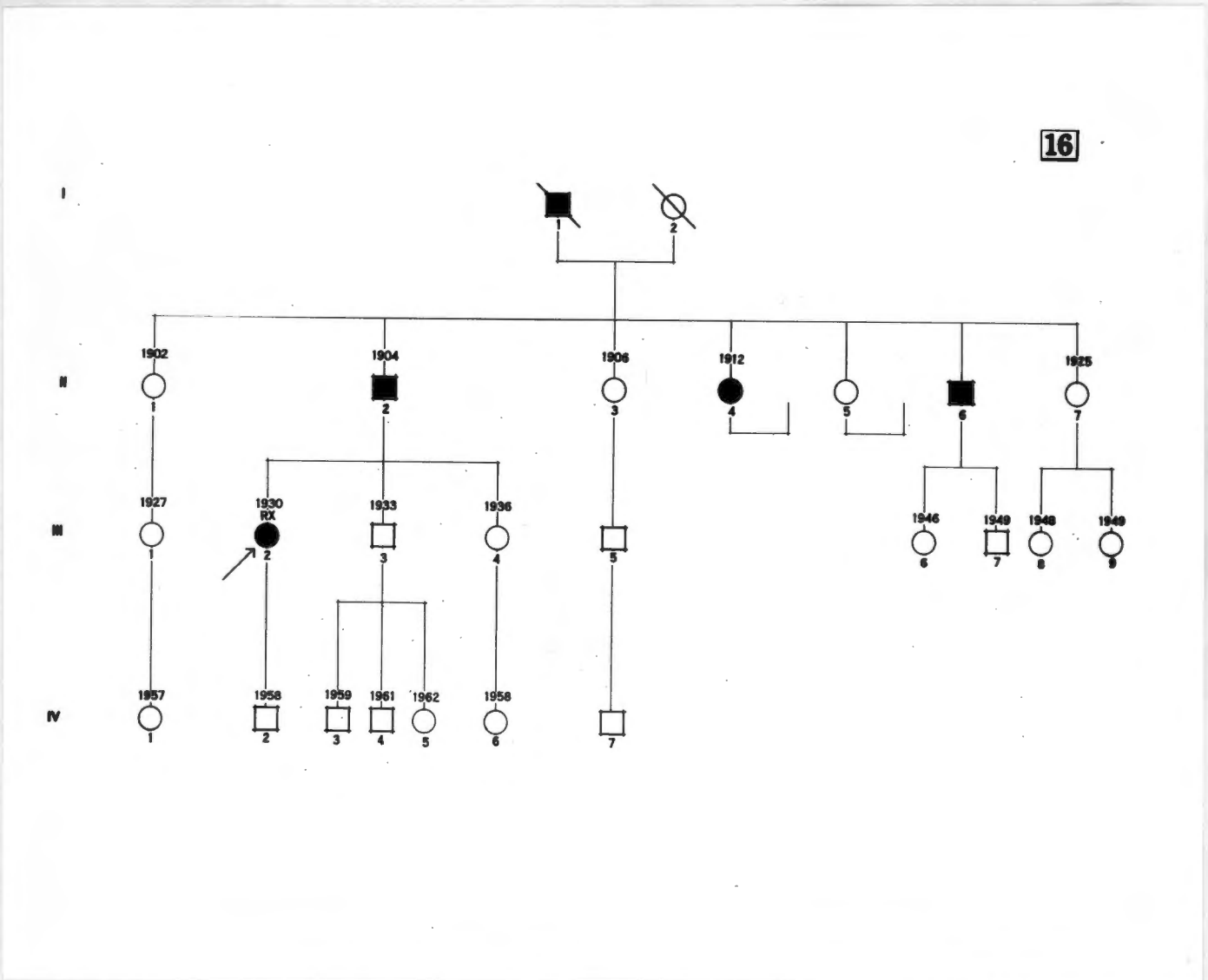
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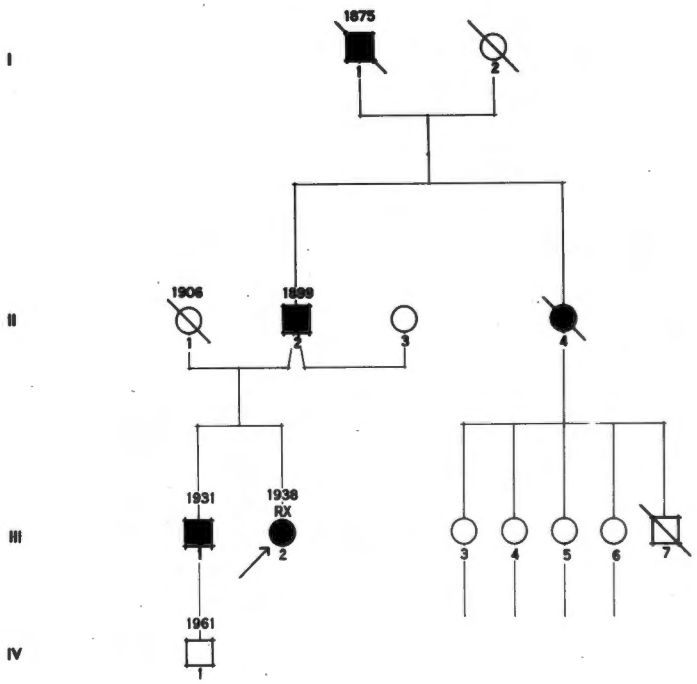

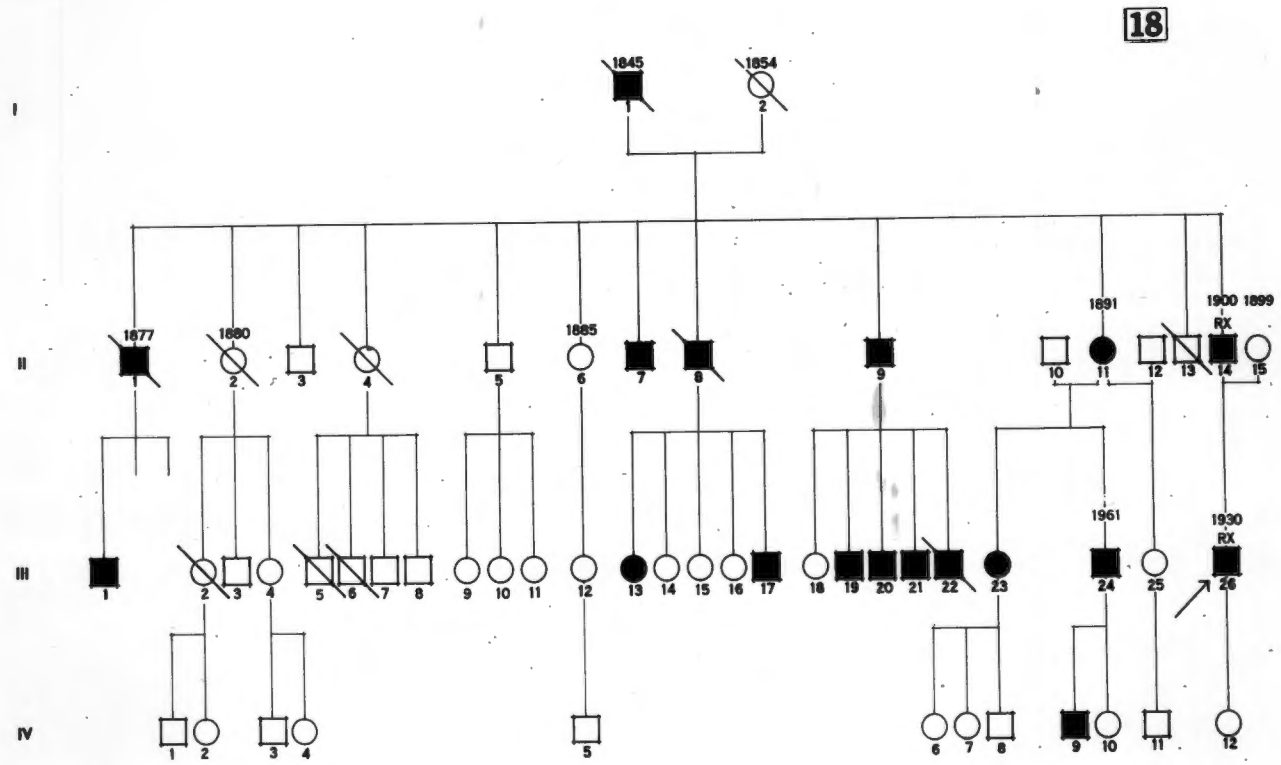
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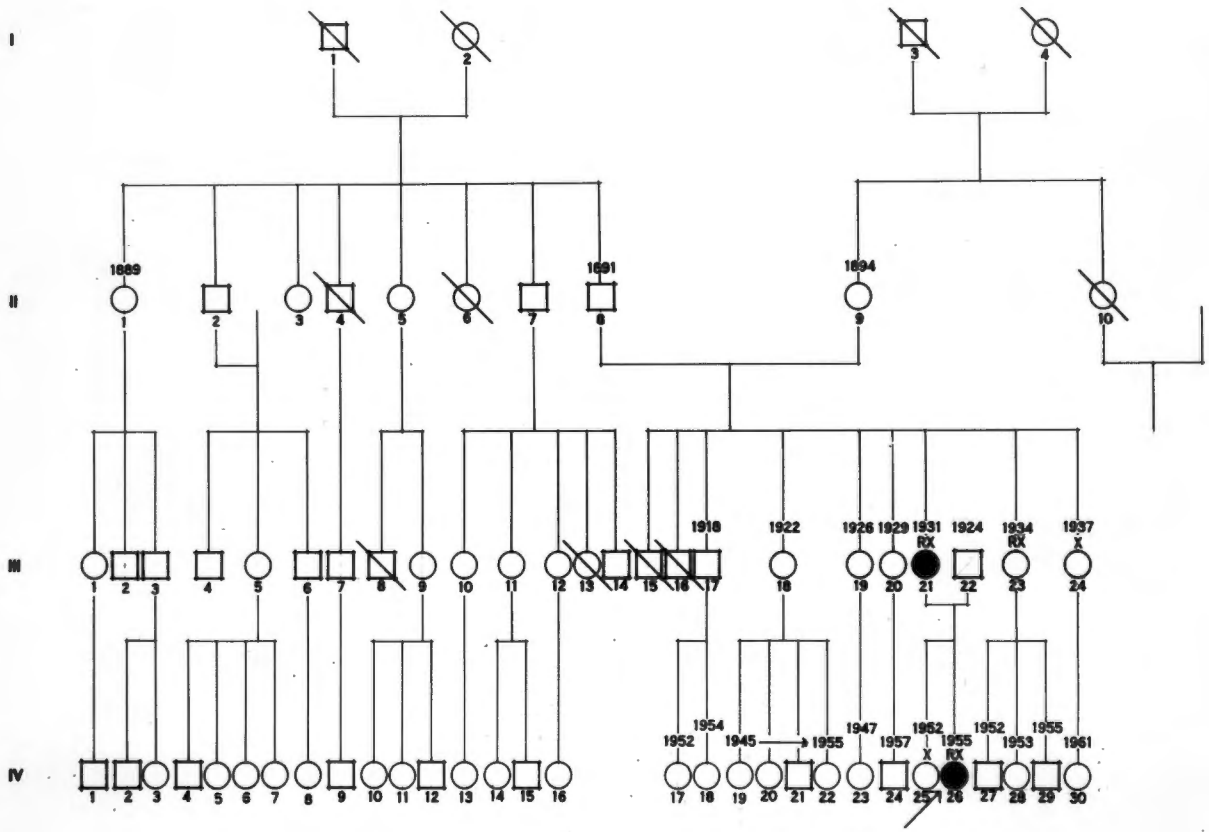
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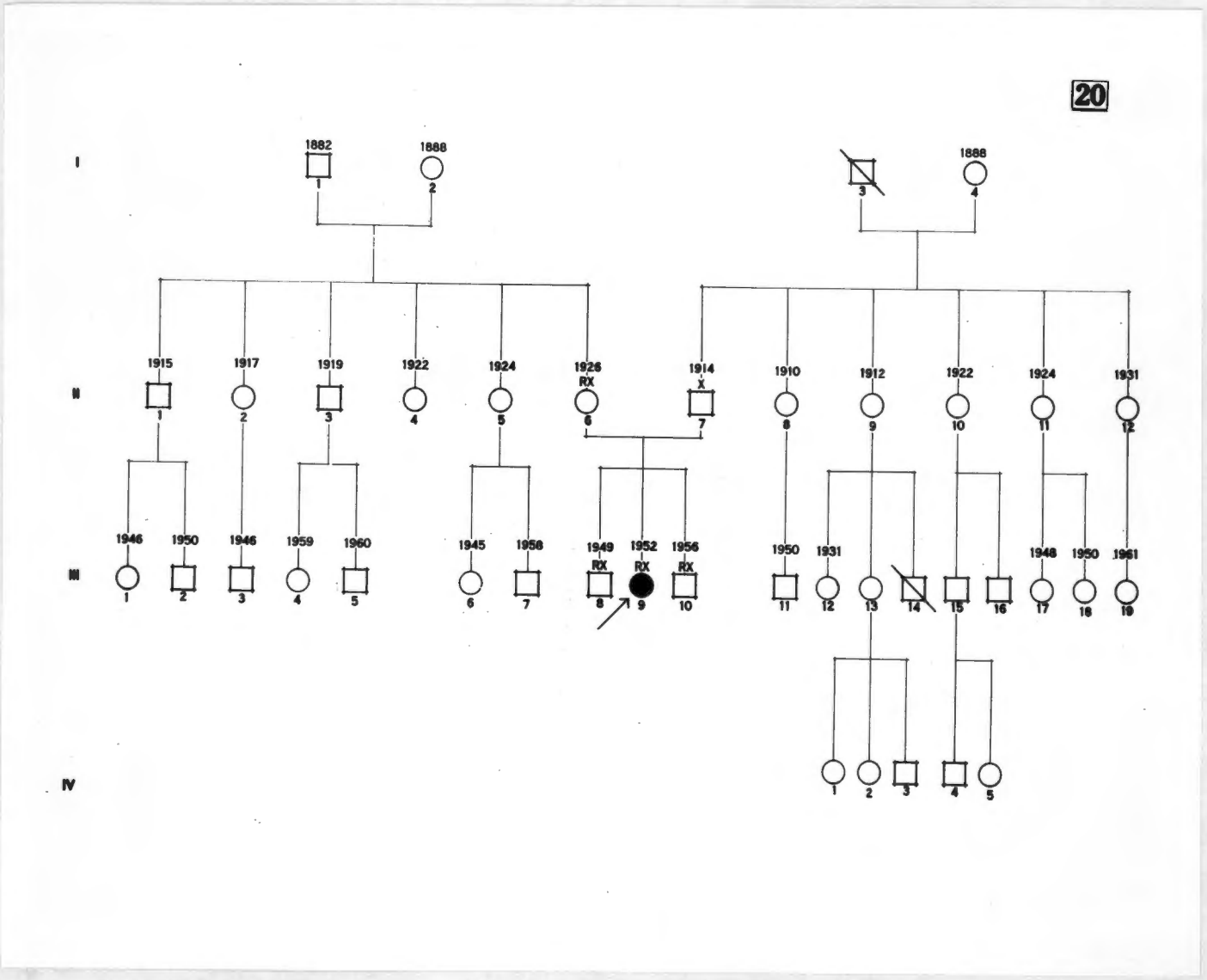
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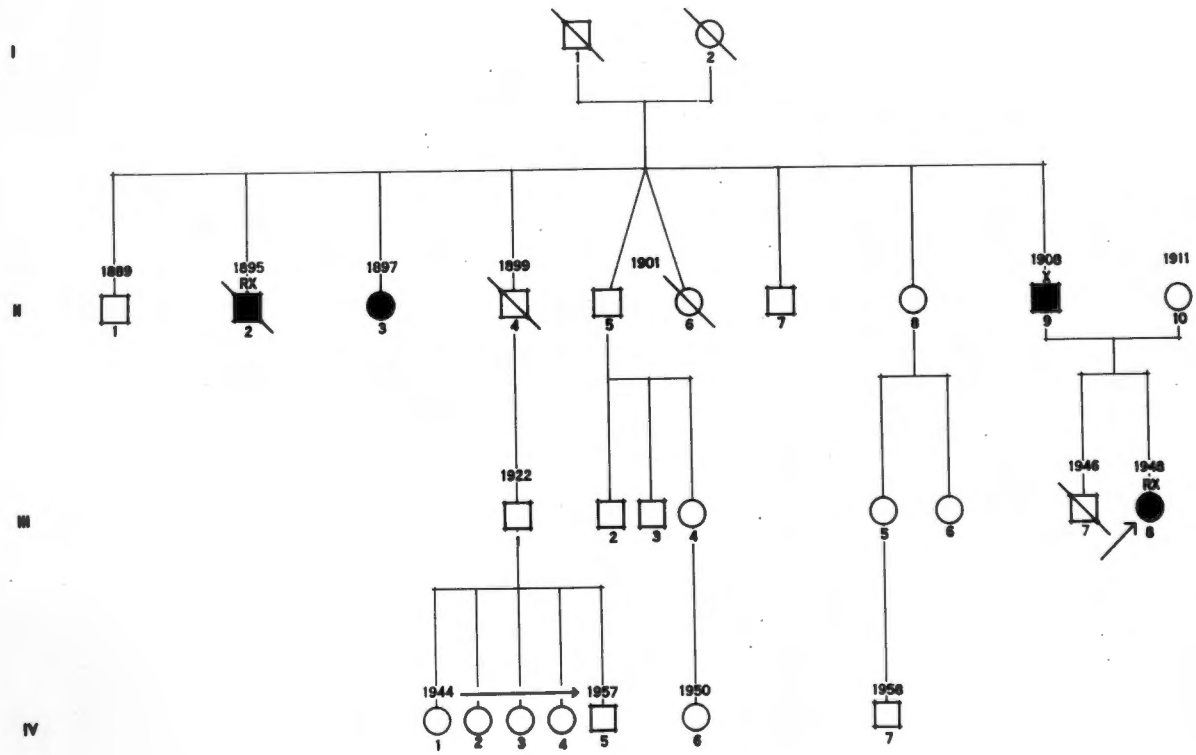
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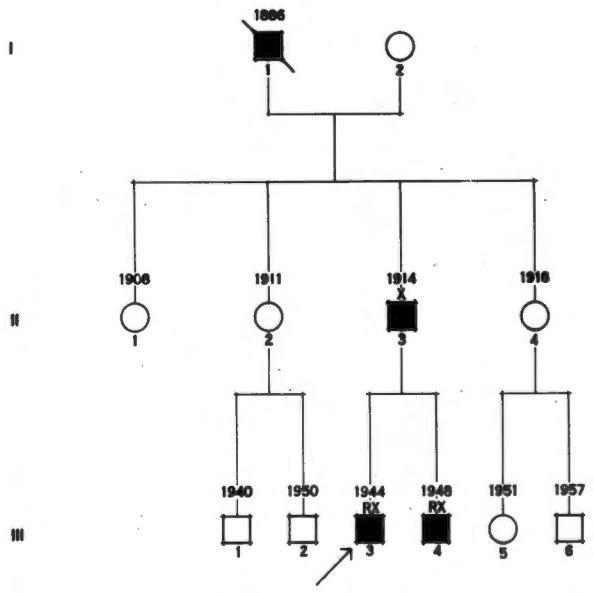
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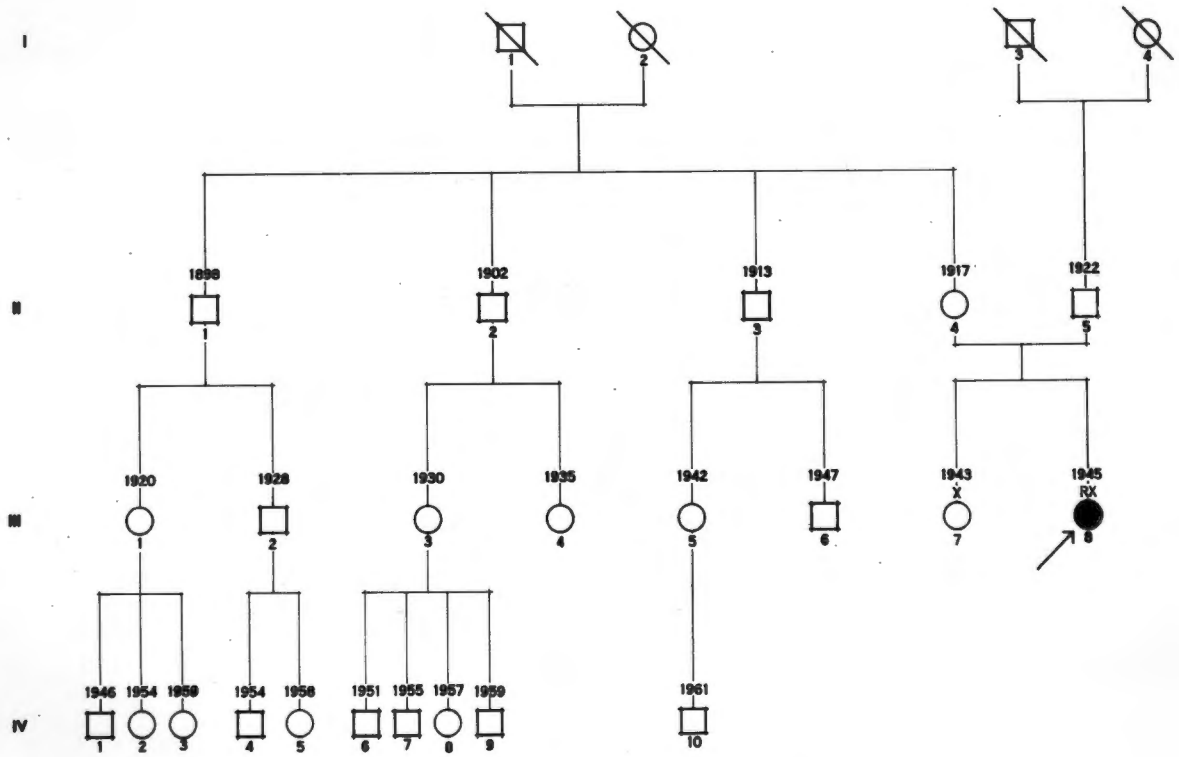
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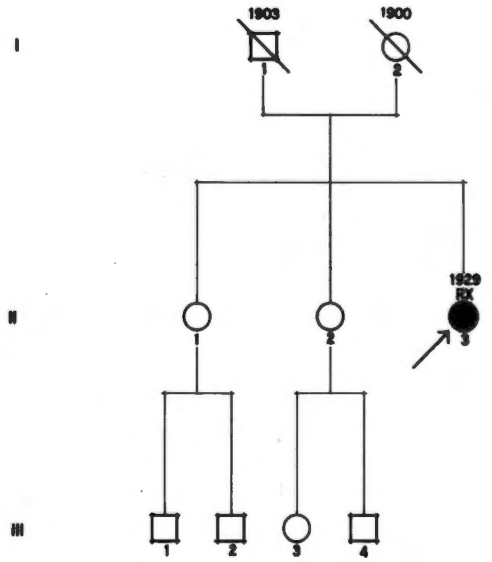

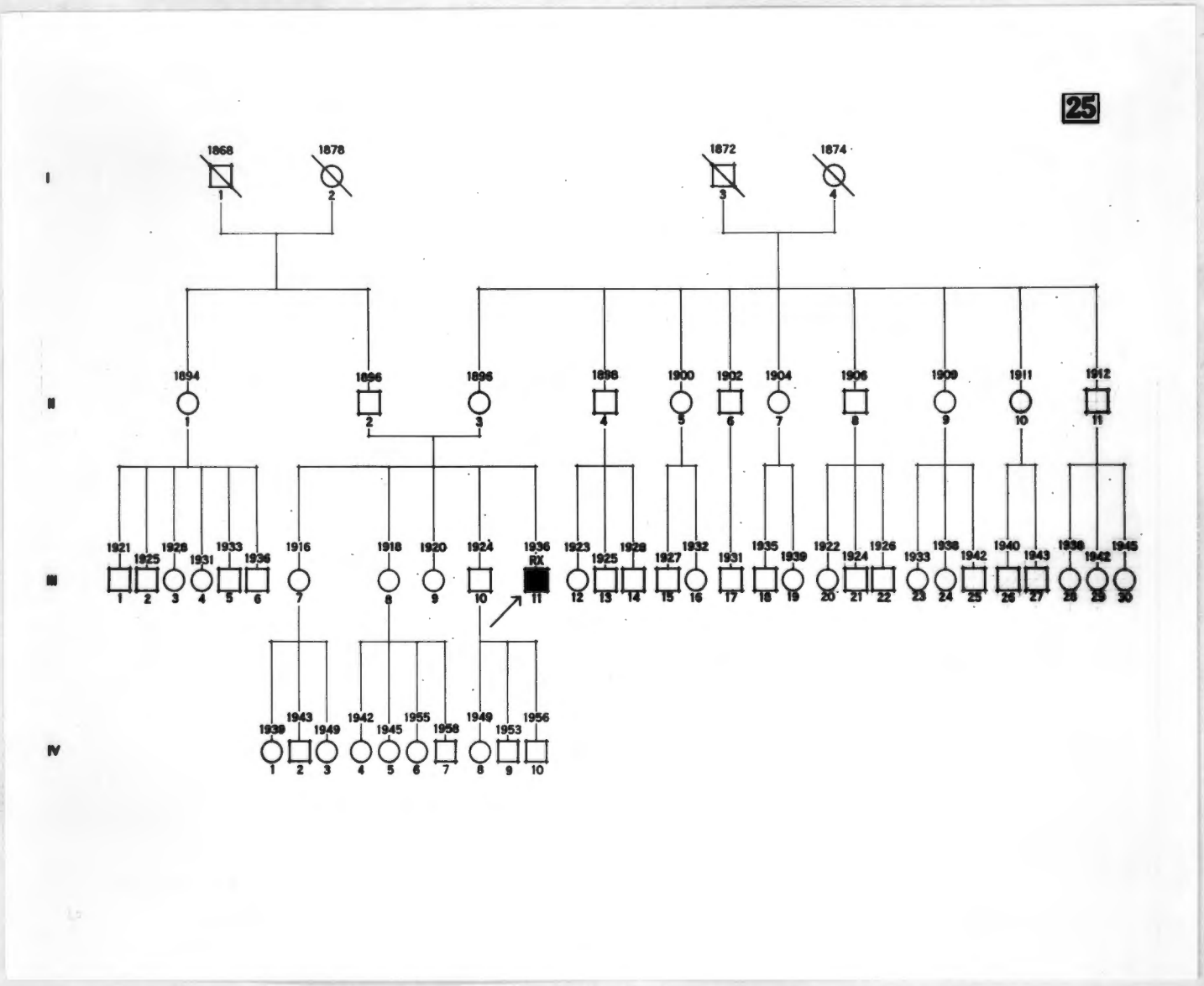
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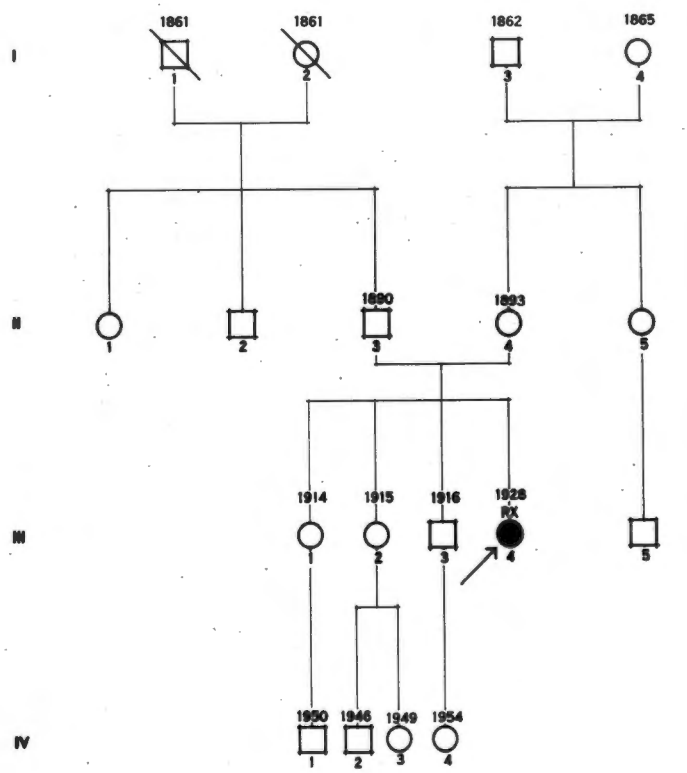
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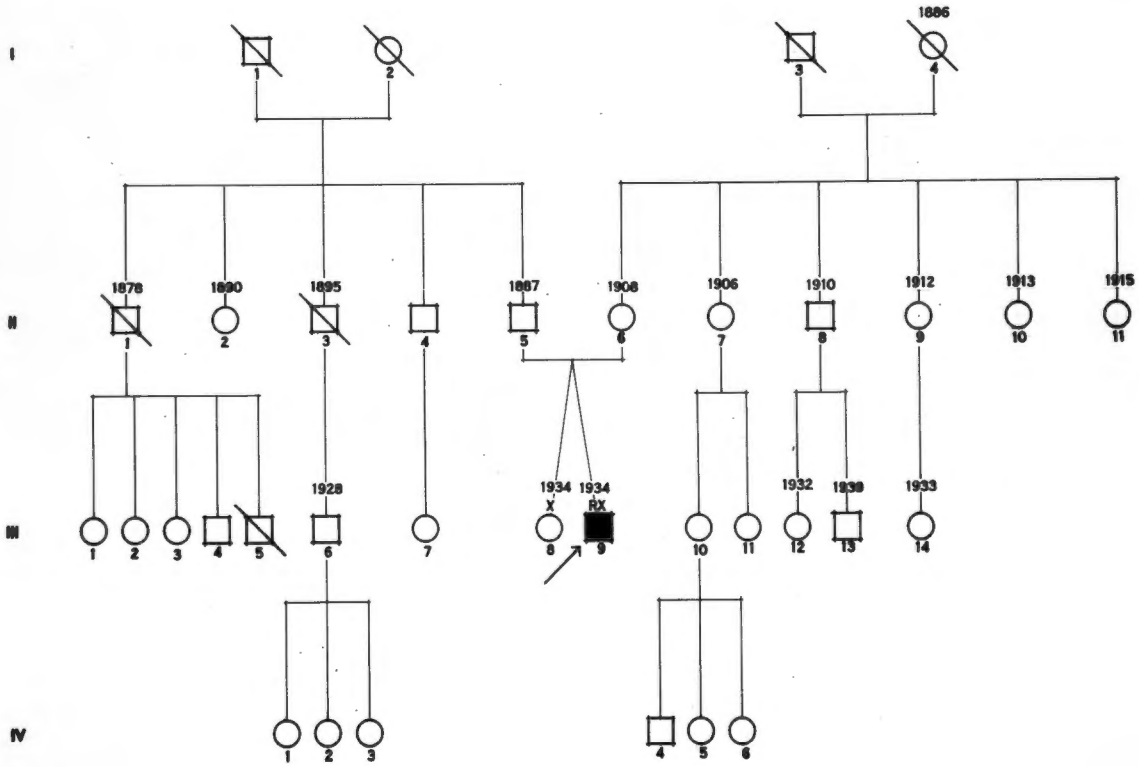
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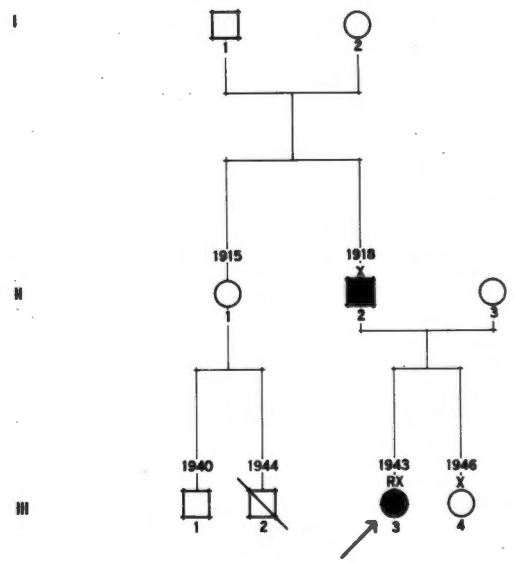

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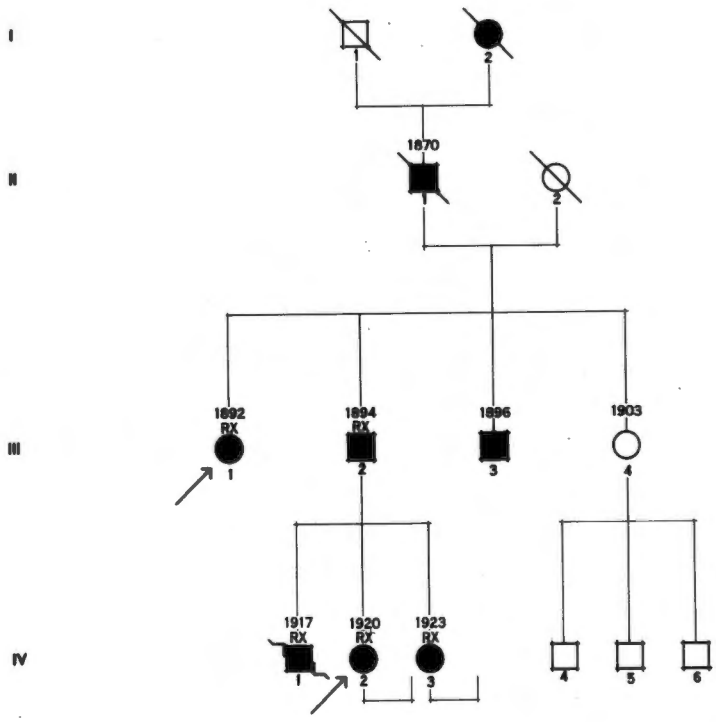
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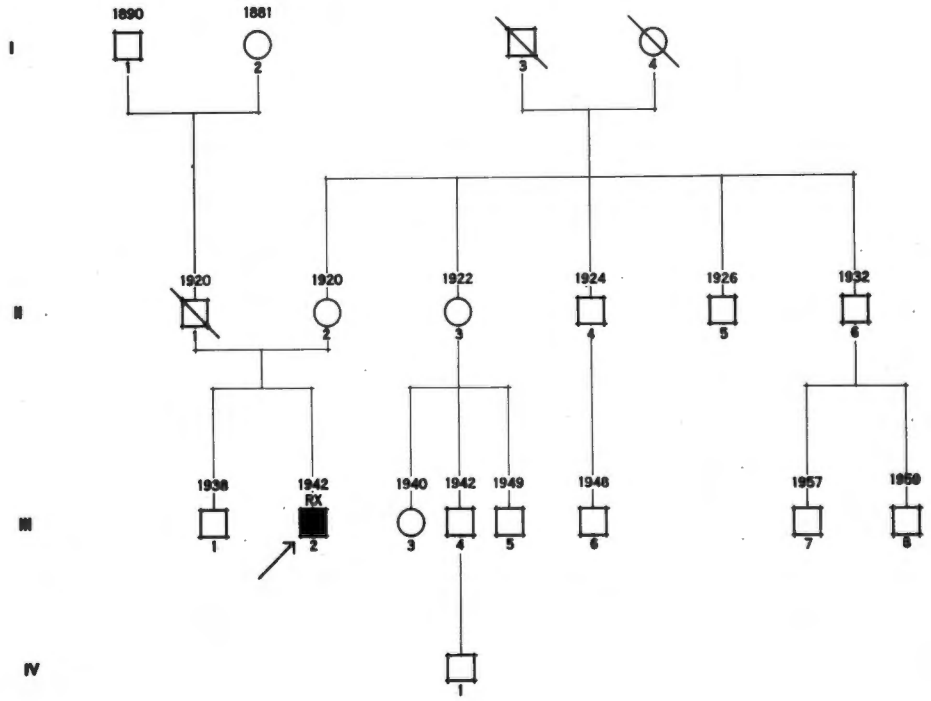
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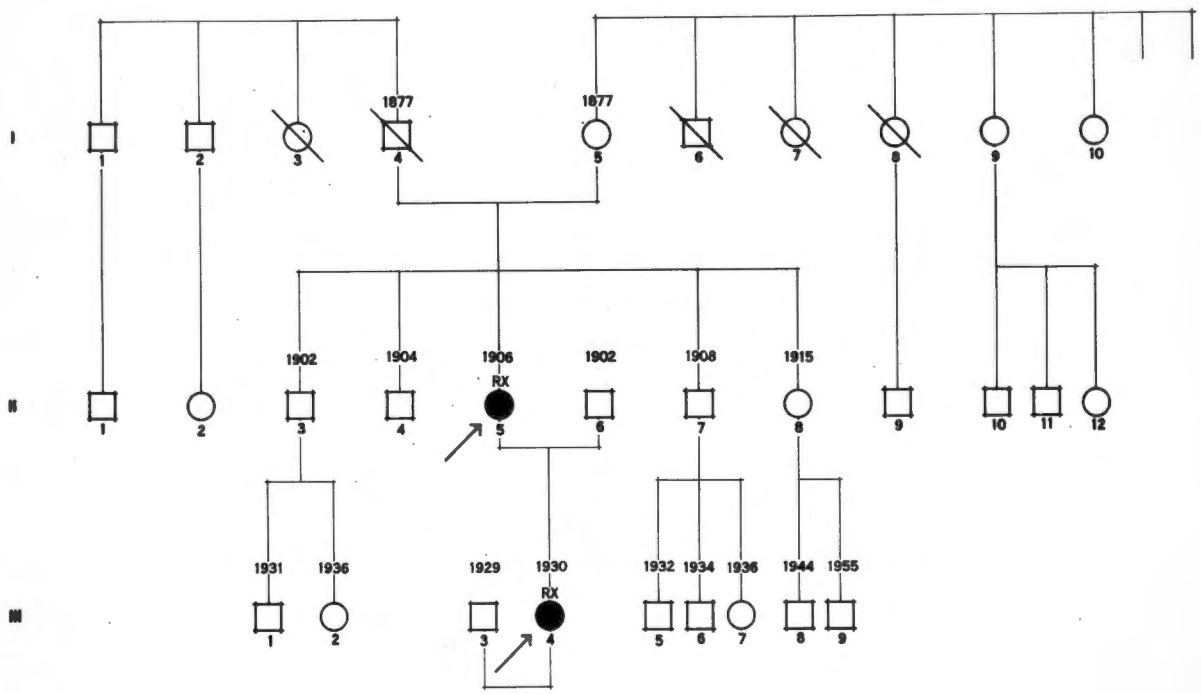
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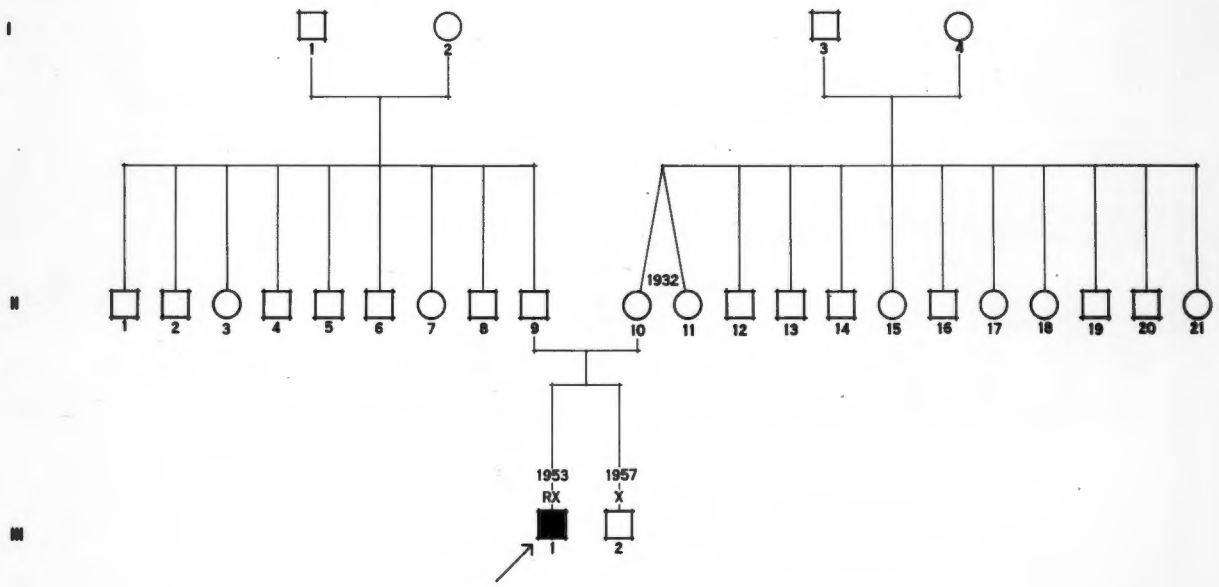
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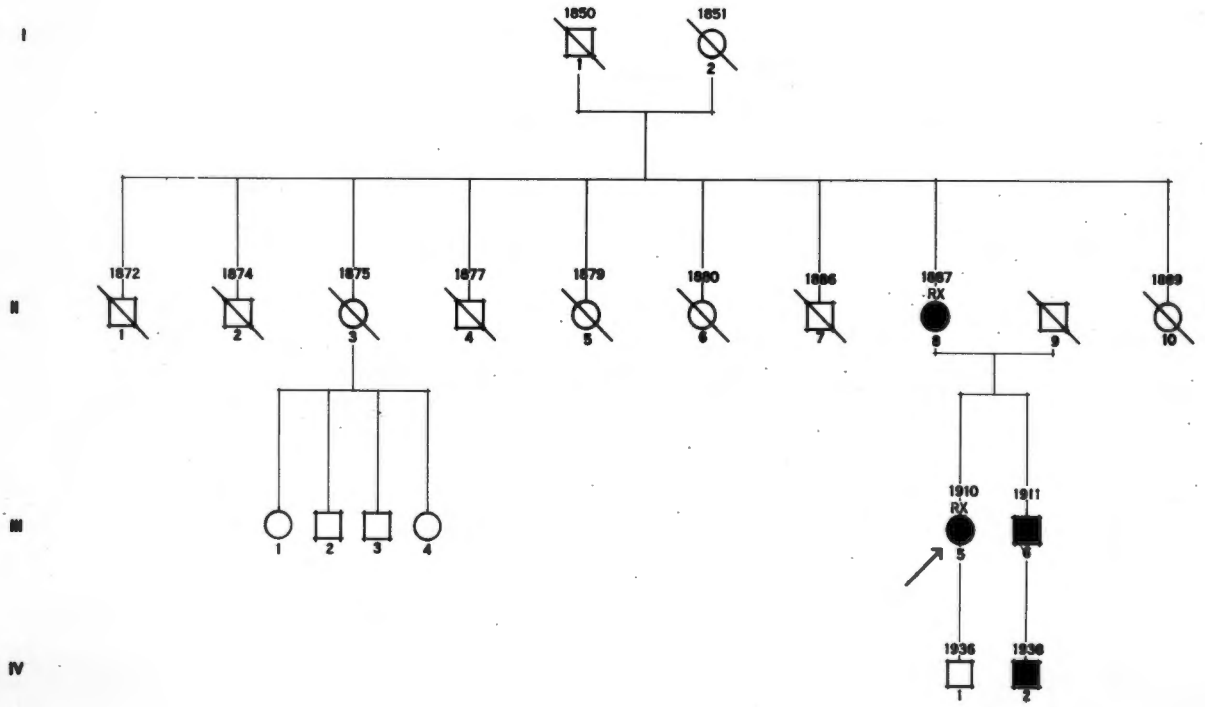
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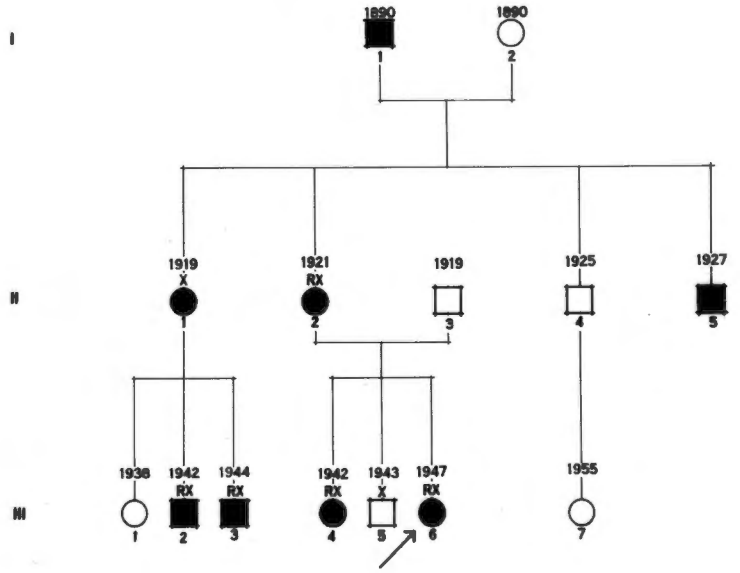
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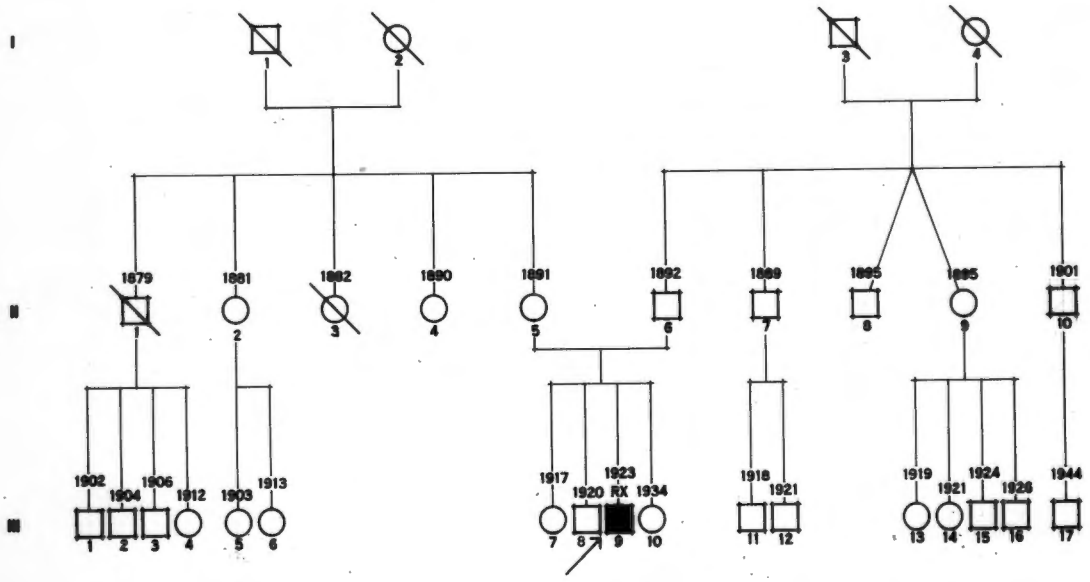
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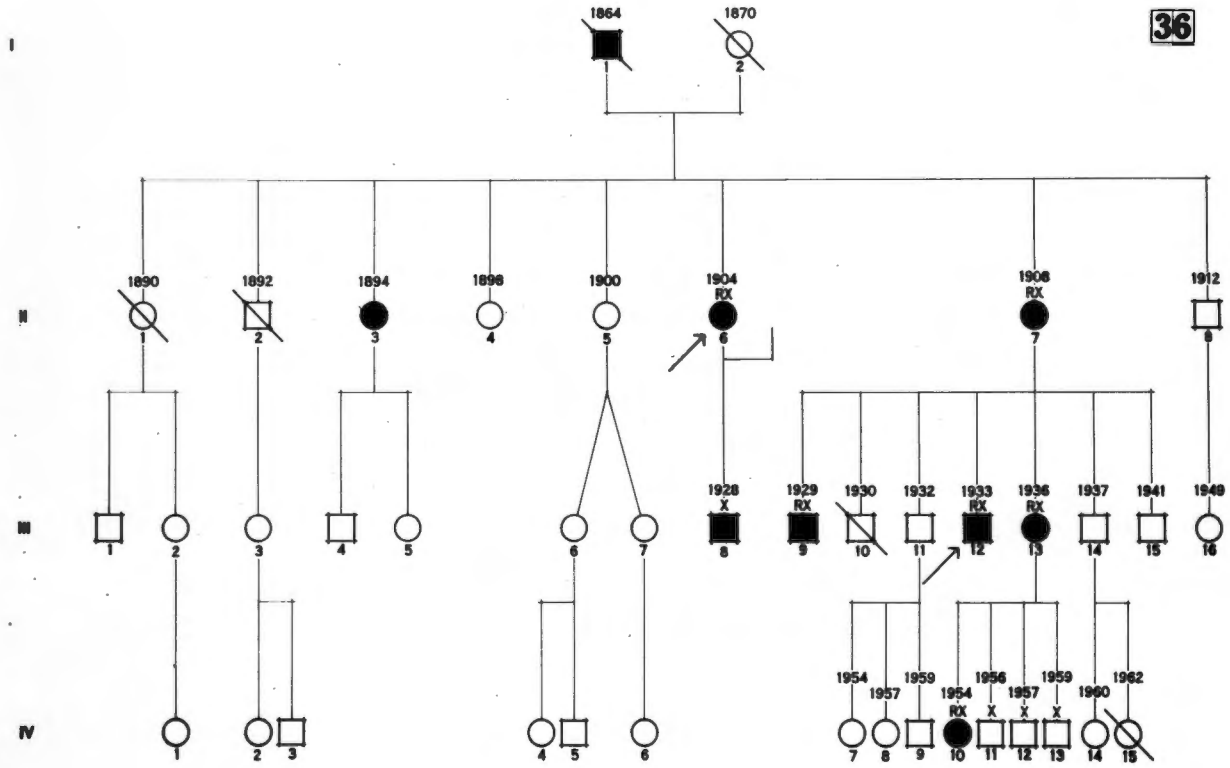
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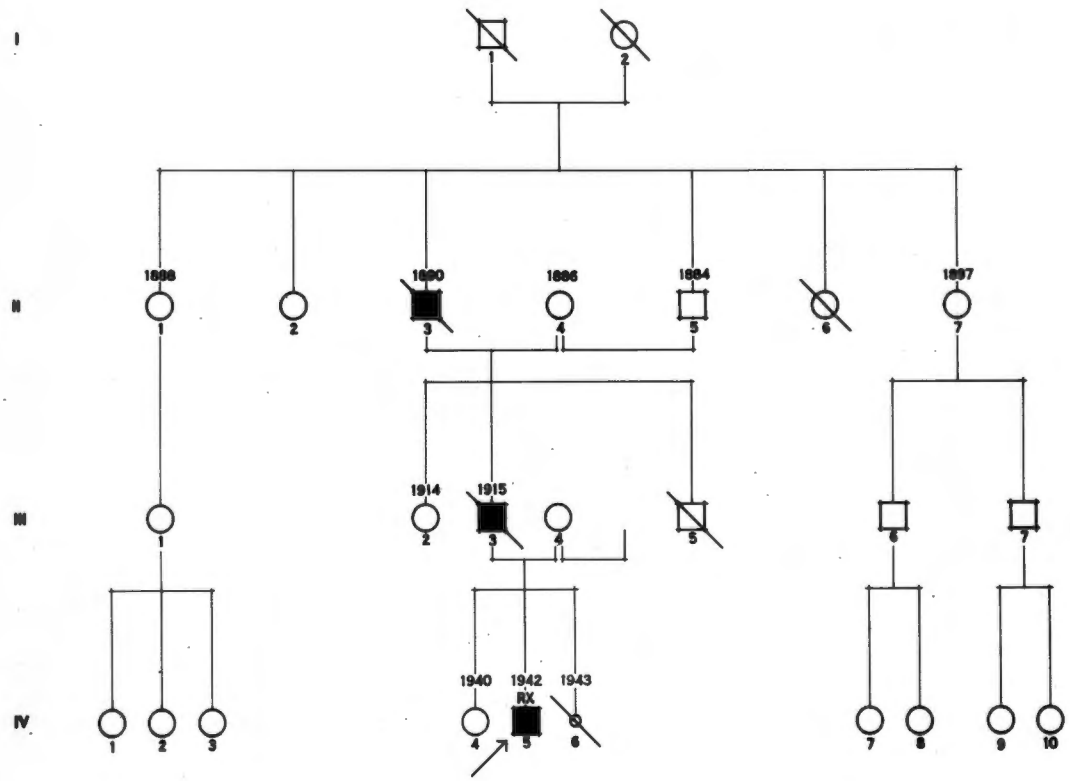
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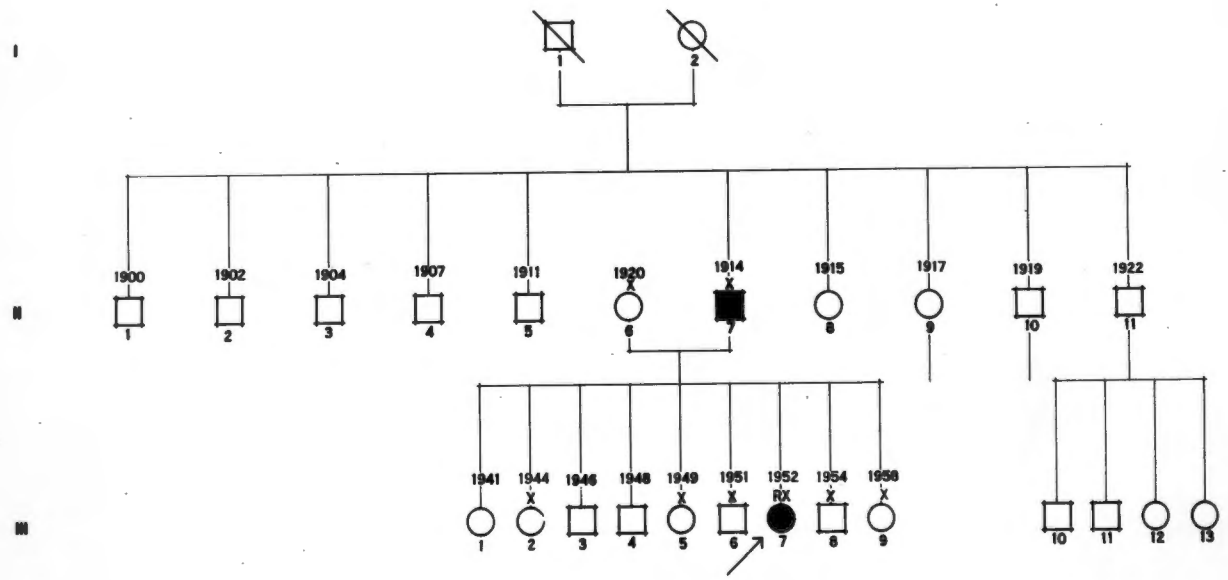
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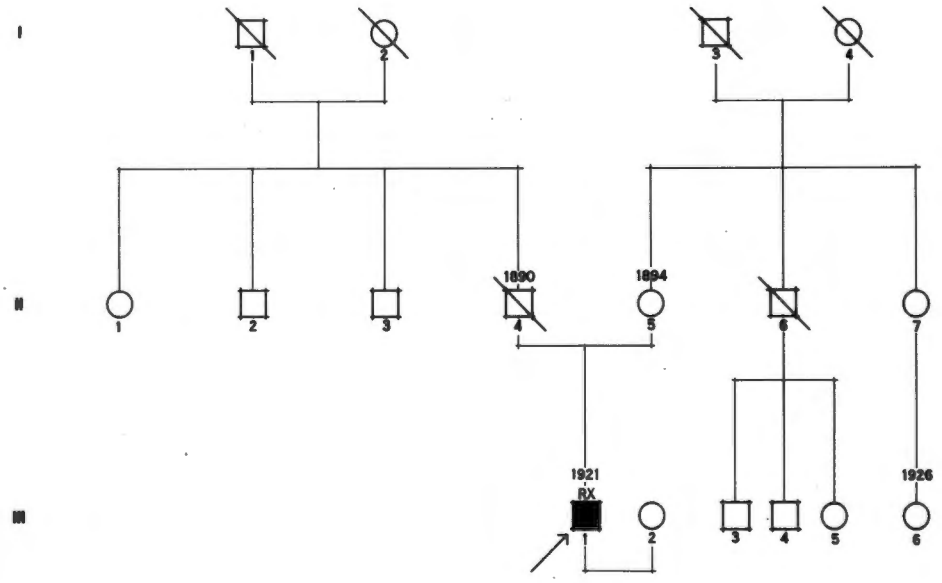

APPENDIX II

SEX INCIDENCE IN DIFFERENT LINES OF INHERITANCE

Pedigree Numbers of Children Affected	ANTECEDENTS AFFECTED											
	Father and Grandfather		Father		Mother and Maternal Grandfather		Father and Paternal Grandmother		Mother		Mother and Grandmother	
	M	F	M	F	M	F	M	F	M	F	M	F
1.	1	1	2	2		1						
2.			1	2								
3.		1	2									
4.			1									
5.				1								
6.									1	1		
7.									1	1		
8.										2		2
9.							3,	2	4	4	1	
10.			1								1	
13.		1	1	1		1						
16.		1	2	1								
17.	1	1	1	1								
18.	7	1	5	1	1	1						
19.										1		
21.				1								
22.	2											
28.				1								
29.	1	2					2	1	1			
31.										1		
33.							1		1	1		
34.			1	2	2	2						
36.				3	3	1						1
TOTALS	12	8	17	16	6	6	6	3	8	11	2	3

APPENDIX III

FREQUENCY OF DIFFERENT PARENTAL GROUPINGS

Pedigree Number	Affected father and unaffected mother	Unaffected father and affected mother	Unaffected father; unaffected but transmitting mother	Unaffected parents transmitter unknown
2 (II)				1
(III)	1			
3 (II)	1			
6 (III)		1		
7 (III)		1		
8 (II)				1
(III)		1		
9 (II)		1		
(III)		1		
(IV)	2			
13 (II)				uncertain
16 (II)	1			
17 (II)	1			
(III)	1			
18 (II)	1			
(III)	2	1		
21 (II)				1
22 (III)	1			
29 (III)	1			
(IV)	1			
33 (III)		1		
34 (II)	1			
(III)		2		
36 (II)	1			
(III)		1		
TOTALS	15	10	0	3

APPENDIX IV

SEX RATIO OF OFFSPRING OF DIFFERENT PARENTAL GROUPS

Pedigree Number	Affected father and unaffected mother		Unaffected father and affected mother		Unaffected father; unaffected but transmitting mother		Unaffected parents; transmitter unknown	
	M	F	M	F	M	F	M	F
1 (II)	2	2						
2 (II)							2	0
(III)	1	1						
3 (II)	2	0						
6 (III)			1	1				
7 (III)			1	1				
8 (II)							0	2
(III)			0	2				
9 (II)			0	2				
(III)			4	4				
(IV)	2	2						
13 (II)	1	1						
16 (II)	2	1						
17 (II)	1	1						
(III)	1	1						
18 (II)	5	1						
(III)	5	1	1	1				
21 (II)							2	1
22 (III)	2	0						
29 (III)	2	1						
(IV)	1	2						
33 (III)			1	1				
34 (II)	1	2						
(III)			2	2				
36 (II)	0	3						
(III)			2	1				
TOTALS	28	19	12	15			4	3

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