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The Concept of Osteoarthrotic Remodelling as Illustrated by Ochronotic Arthropathy of the Hip

An Anatomico-Radiological Approach

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Summary. This report is an anatomico-radiological study of six femoral heads excised from four patients with diffused ochronotic arthropathy. In one case a biopsy specimen taken eleven years earlier was also studied.

The deterioration of the ochronotic cartilage involves a fragmentation process reflected by histological characteristics that are different from those observed in common "cartilaginous degeneration". The fragments resulting from this process become embedded in the remodelled bone-marrow tissue of the weight-bearing zone and in the synovial membrane. Except for the presence of pigmented cartilage, the intrinsic osteogenic remodelling and the extrinsic osteophytic remodelling (the latter often appearing in the form of minor equivalents) are similar to that of the common form of osteoarthrotic remodelling.

The pigment labelling of the ochronotic cartilage provides a particularly favorable opportunity to study the general problem of osteoarthrotic remodelling; it facilitates the differentiation between newly formed and preexisting tissue and consequently our understanding of the entire process.

An anatomico-radiological approach provides an explanation for the similarity frequently observed on X-rays between ochronotic and rheumatoid hip arthropathies.

Key words: Ochronosis – Ochronotic arthropathy – Osteoarthritis – Hip ochronotic arthropathy – Hip osteoarthritis.

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„Die Gelenkknorpel zeigten die Erscheinungen des sogenannten Malum senile (Arthritis deformans)... Außen um mehrere Gelenke fanden sich allerlei osteophytische Bildungen".
Rudolph Virchow – Archiv Path. Anat. **37**, 1866.

In Virchow's first article on ochronosis, in which he reported the presence of pigmentation in various kinds of cartilage, the similarity of certain articular modifications to those characteristic of osteoarthritis was already mentioned. These findings are well known today through X-ray and occasional anatomical observations particularly with regard to the three peripheral articulations most frequently affected by ochronosis, i.e., knee, shoulder and hip.

The articular deposits of ochronotic pigment provide an excellent model for a better general understanding of the nature of osteoarthritic remodelling. In the present paper, this will be illustrated with surgical specimens which have also been used in another anatomico-radiological study performed in collaboration with Steiger (Lagier and Steiger, in press).

Material and Methods

Our observations are based on a study of seven specimens corresponding to six femoral heads excised from four patients with diffuse ochronotic arthropathy, in the course of surgery for hip replacement. Acetabular material was studied only in specimen VII.

Specimens I (T. 12638/67) and II (T. 9662/68) correspond to the right and left hip respectively of a 65 year-old woman with diffuse ochronotic arthropathy. Signs of bilateral hip arthropathy had only become apparent at the age of 64; X-ray revealed significant erosion in 6 months for the right hip and in one year for the left.

Specimens III (T. 5232/75) and IV (T. 5233/75) were excised from a 65 year-old woman with diffuse ochronotic arthropathy (David-Chaussé et al., 1978). Signs of bilateral hip arthropathy had appeared at 61 years and a protrusio acetabuli began to develop.

Specimen V (T. 8104/61) correspond to a right femoral head excised from a 49 year-old man, clinically known only as a patient with ochronotic arthropathy.

Specimens VI (T. 299/57) and VII (T. 3437/68) were both excised from the right hip of a man who had been affected in that hip from the age of 32 and in the left hip as well from the age of 56 (Martin and Meyer, 1961). Specimen VI was obtained in the course of a curettage-packing performed when the patient was 52 (method of Camera). Because of extreme stiffness of the hip caused by osteoarthritis, hip replacement was performed when the patient was 63, at which time specimen VII was excised.

Each specimen was X-rayed, decalcified and embedded in paraffin (except for specimen VII, which was embedded in celloidin). Sections were stained by haematoxylin-eosin (HE), van Gieson, Nile blue and Alcian blue; others were left unstained and studied both before and after treatment with H_2O_2.

Results

All of the specimens showed essentially similar basic lesions and in each case the association of these lesions constituted an osteoarthrotic remodelling. Mirror-image lesions were observed in acetabular material of specimen VII.

The preexisting articular cartilage showed extra-cellular ochronotic impregnation with characteristic properties. It appeared ocher in color in the unstained

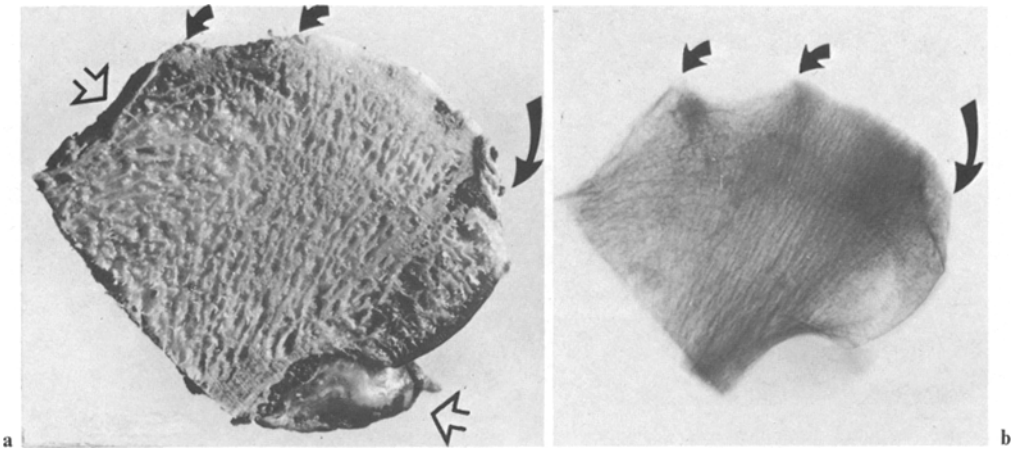

Fig. 1a and b. Specimen I. Right femoral head, posterior half. **a** Macroscopic aspect of the cut surface ($\times 1.2$); **b** X-ray ($\times 1$). Eburnated bone surface visible between the medial short arrow and the long arrow, and eroded bone surface between the two short arrows. The long arrow indicates the fovea capitis with stump of ochronotic ligament of the head. The cartilage beneath the fovea capitis can be seen to be ochronotic. The wide arrowheads indicate ochronotic cartilage fragments embedded in the synovium

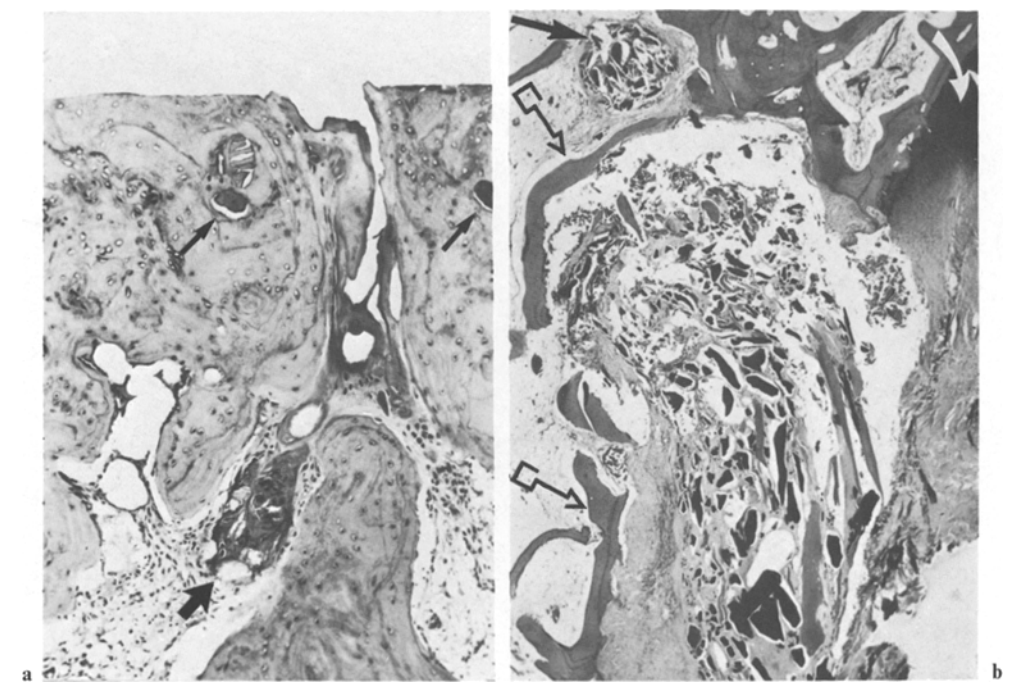

Fig. 2a and b. Specimen I. Microscopic aspect (HE). Histological details. **a** ($\times 60$) remodelled bone of the eburnated zone (upper border represents the outer surface of the head) showing embedded ochronotic cartilage fragments (thin arrows) and area of aseptic medullary necrosis (thick arrow). The empty osteocytic cavities indicate necrosis of the superficial osteocytes. **b** ($\times 10$) remodelled foveal region. Outlined arrows indicate the bony border of the concavity. Fragments of ochronotic cartilage are embedded in a small intra-osseous area (long black arrow) as well as in the synovial tissue. The curved white arrow indicates the ligament of head

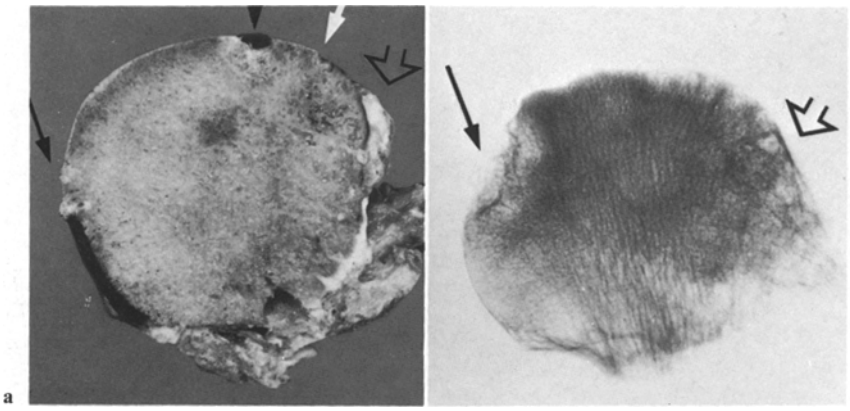

Fig. 3a and b. Specimen II. Left femoral head, section of posterior quarter. **a** Macroscopic aspect of the cut surface (×1); **b** X-ray (×1). Superior-medial region showing eburnated surface with remnant of ochronotic cartilage fragment (black arrowhead). Thin black arrow indicates the foveal region. Beneath the fovea, cartilage is ochronotic. Wide arrowhead indicates synovial overgrowth on a thin layer of ochronotic cartilage, flanked by a subchondral bony cortex. The white arrow is explained in Fig. 4b

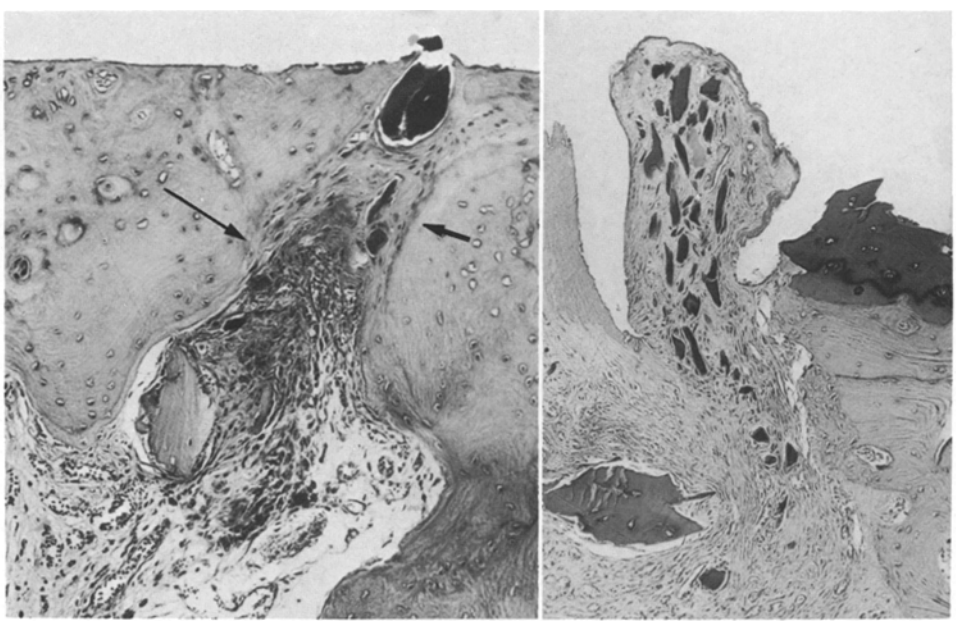

Fig. 4a and b. Specimen II. Left femoral head, weight-bearing zone. Microscopic aspect. Histological details (HE). **a** (×90) Remodelled bone tissue of the eburnated zone (upper border represents the outer surface of the head) showing embedded ochronotic cartilage fragments (short arrow); some of which are in contact with areas of aseptic medullar necrosis (long arrow). The empty osteocytic cavities indicate necrosis of the superficial osteocytes. **b** (×61) Detail of area indicated on Fig. 3a by white arrow. Right side, remaining bone cortex covered by a thin layer of ochronotic cartilage. Left side, fibrous mass and superficial outgrowth containing embedded fragments of ochronotic cartilage

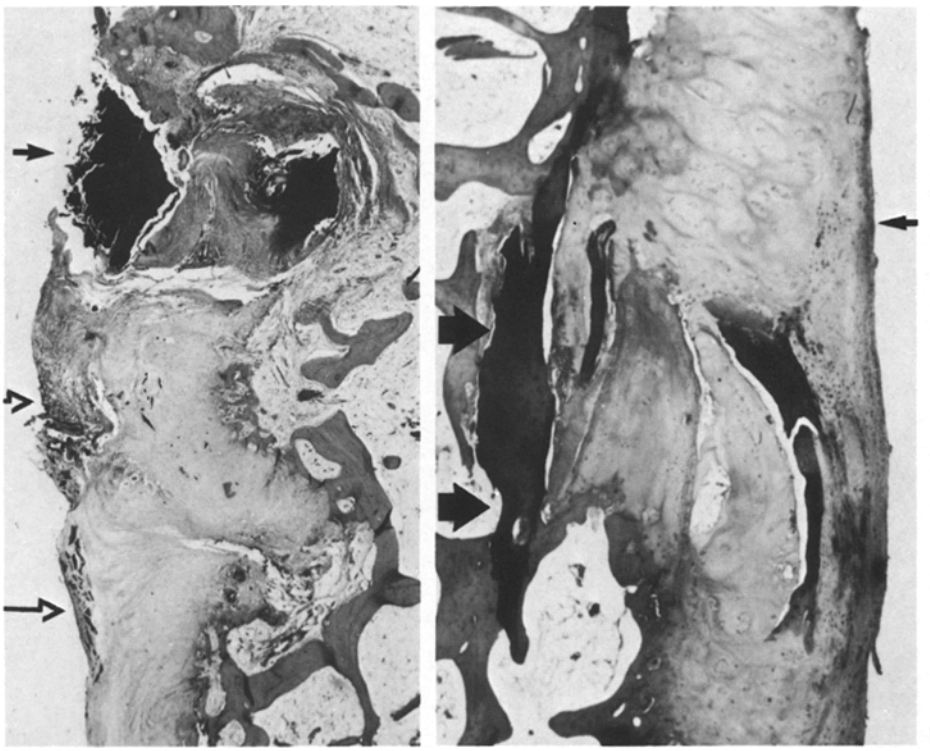

Fig. 5a and b. Specimen II. Left femoral head, non-weight-bearing zone, section more frontal than that shown in Fig. 3. Microscopic aspect; histological details (HE). **a** (×10) Foveal region. Black arrow indicates fragments of the ligament of head partly embedded in scar tissue. The outlined arrows indicate fibrocartilaginous covering under the fovea; it contains fragments of ochronotic cartilage, occasionally deeply embedded, but principally in the surface pannus. **b** (×20) Superficial area indicated by the wide arrowheads shown in Fig. 3. Cartilaginous covering containing embedded strips of preexisting ochronotic cartilage. Thick arrows indicate the lower boundary of preexisting ochronotic cartilage. The thin arrow is explained on Fig. 6

sections, blue green after staining with Nile blue, dark brown after staining with haematoxylin-eosin or van Gieson. The ocher color on the unstained sections disappeared after treatment with H_2O_2. The pigmentation was complete in some parts, while in others pericellular territories were not affected (as indicated by blue halo around chondrocytes on Alcian blue stained sections). The break-down process caused by the pigment impregnation could explain the numerous small fragments with sharp edges and no cellular proliferation (Fig. 13) as well as the more or less complete destruction of the cartilage in the weight-bearing zone (Figs. 1, 3, 7, 8, 12).

The bone of the weight-bearing zone is thus laid bare over a large surface and reacts by osteogenic remodelling. The resulting eburnated bone is essentially composed of lamellar tissue which is abraded and necrotic at the surface (Figs. 2a, 4a, 9a); in specimen VII, the eburnated zone extends beyond the top of the osteophyte in a previously non-weight-bearing zone (Fig. 12). The

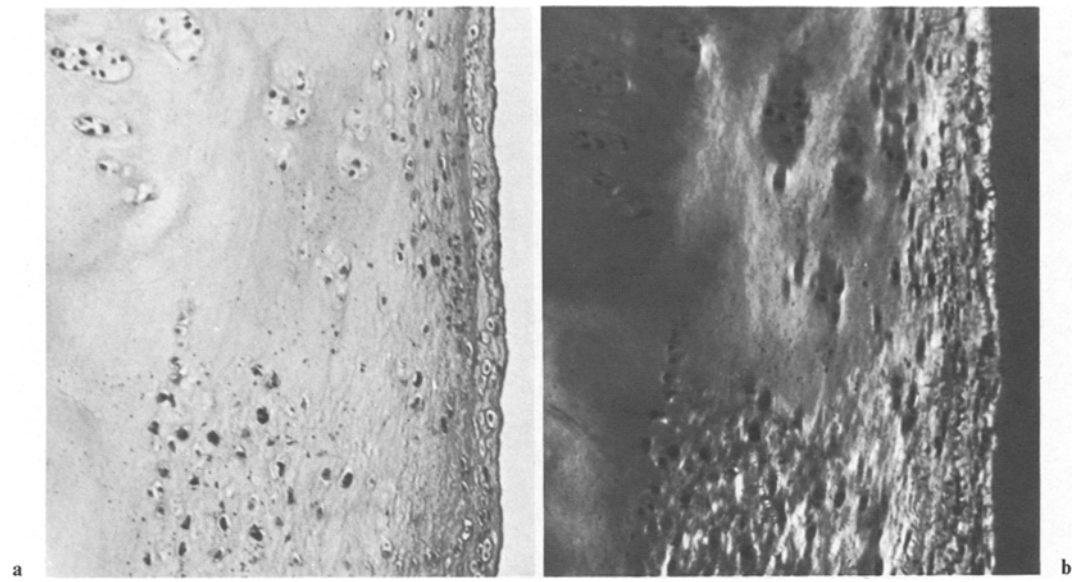

Fig. 6a and b. Specimen II. Left femoral head, microscopic aspect (HE × 56). Histological detail of the area indicated by the thin arrow in Fig. 5b but on a more frontal section. **a** Unpolarized light; **b** polarized light. Incomplete dedifferentiation of the hyaline cartilage with cell proliferation and absence of intercellular ochronotic pigment characterize the upper part of the figures and the areas presenting the deeper parts of the cartilage. More complete dedifferentiation with intracytoplasmic ochronotic deposits and fibrous structure can be seen near the cartilage surface and in the lower parts of the figures. Numerous pigmented grains scattered during the cutting of sections can be seen

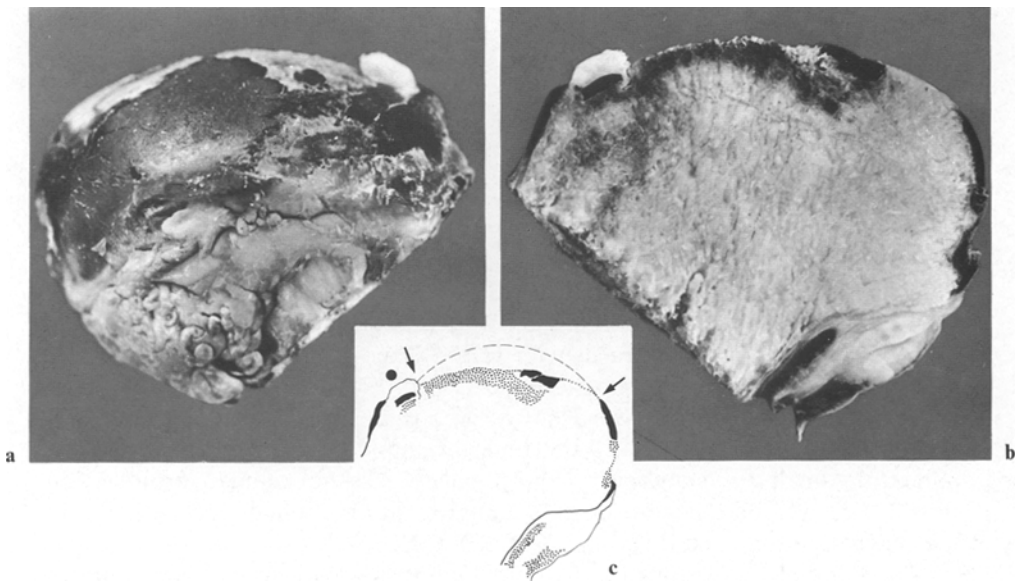

Fig. 7a–c. Specimen V. Right femoral head, posterior half. Macroscopic aspect showing uneven erosion of the ochronotic cartilage covering. **a** Posterior side (× 1.1). **b** Cut surface (× 1.1). **c** Diagram of cut surface shown in **b**. Broken line traces the contour of the normal femoral head. Black areas represent remnants of ochronotic cartilage. Black point situates one of these remnants covered with connective tissue. The two arrows define extent of eburnated remodelled surface. Dotted areas indicate presence of embedded ochronotic cartilage fragments in the bone or synovium

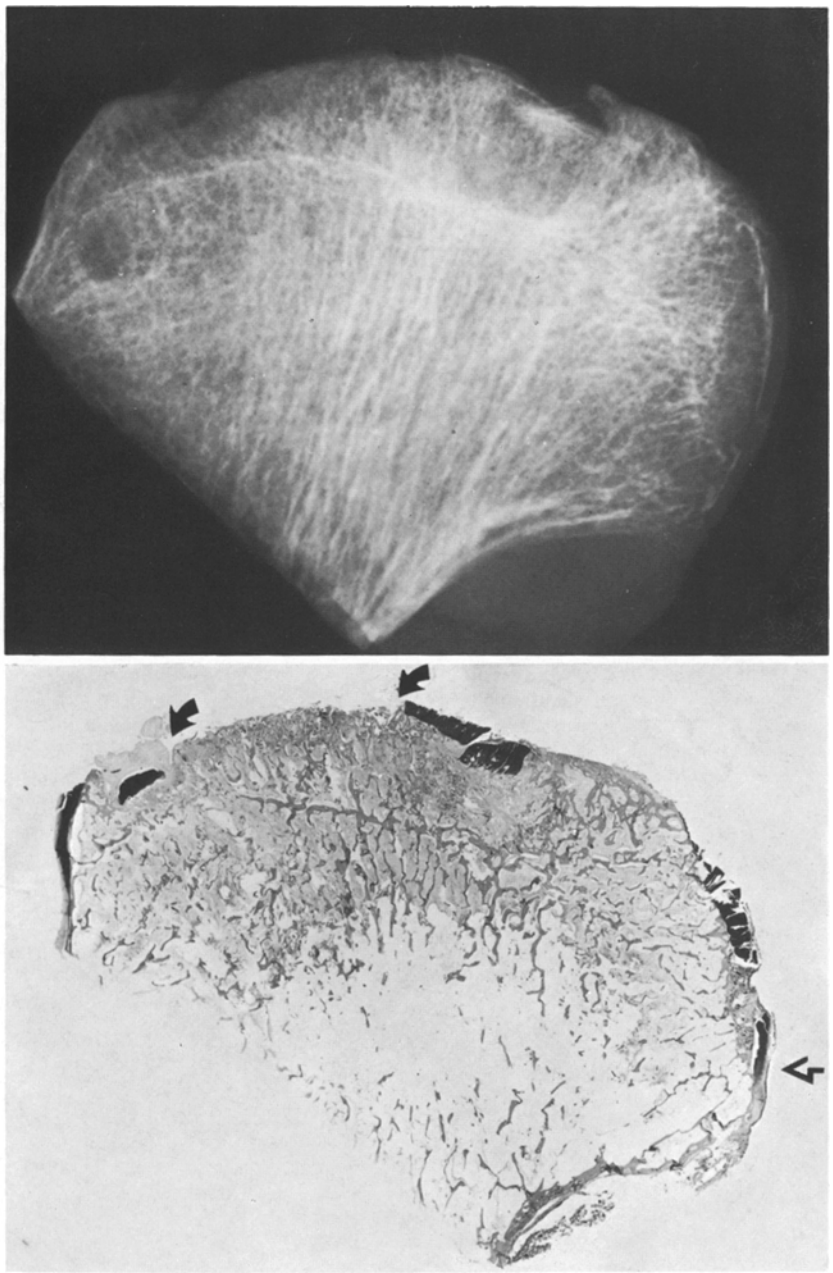

Fig. 8a and b. Specimen V. Radiological and microscopic aspect of half of the femoral head shown in Fig. 7 (× 1.9). **a** X-ray; **b** Histology. The outlined arrowhead indicates a pannus covering ochronotic cartilage beneath the fovea (the short curved arrows are explained in Fig. 9)

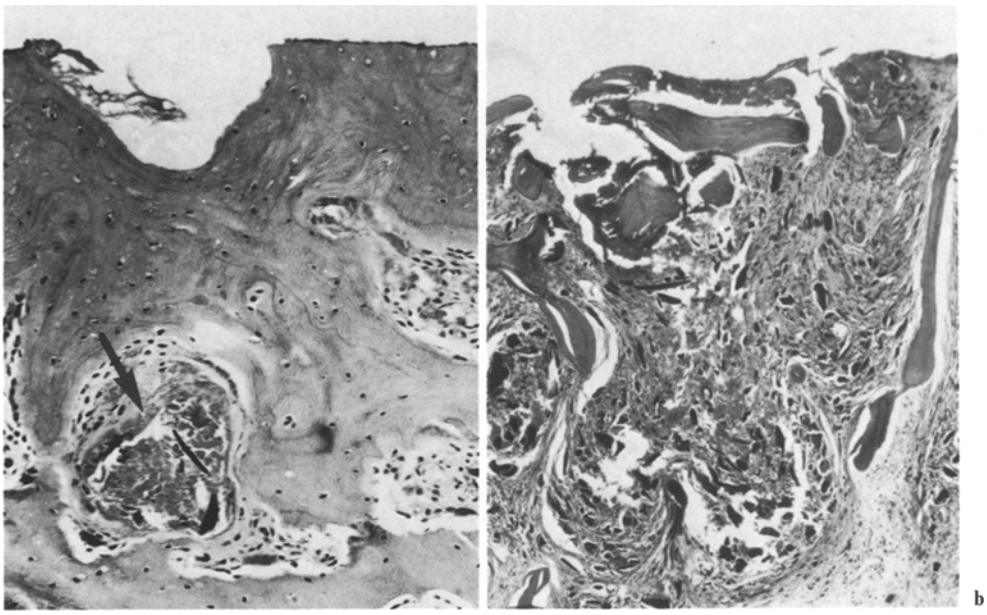

Fig. 9a and b. Specimen V. Microscopic details of eburnated zone between the two short curved arrows shown in Fig. 8b (HE × 28). **a** Above, outer surface. Remodelled bone with fibrous marrow in which a necrotic area (indicated by the arrow) containing ochronotic cartilage fragments. **b** Another microscopic view of the eburnated zone between the two short curved arrows on Fig. 8b showing pocket of necrosis open on the outer surface and bordered elsewhere with connective tissue. In this pocket, dead bone fragments and, deeper, ochronotic cartilage fragments with phagocytosing cells

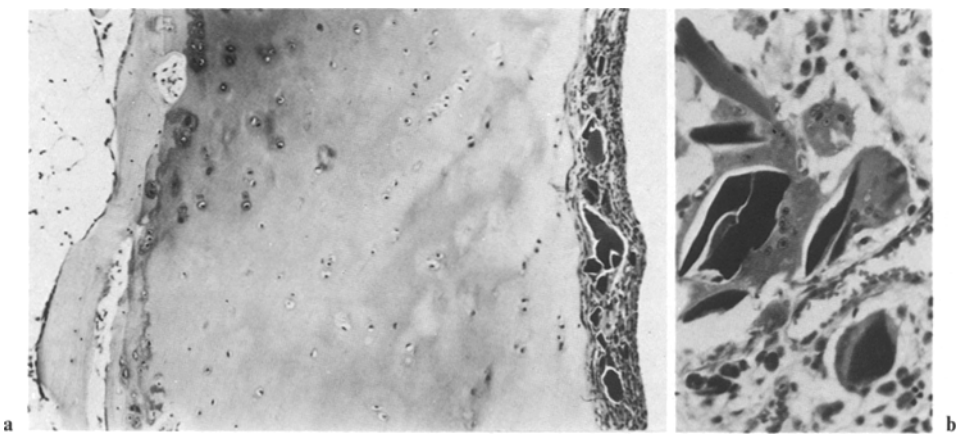

Fig. 10a and b. Specimen V. Other microscopic details (HE) from Fig. 8b. **a** (×65) Ochronotic fragments embedded in a pannus covering a relatively unpigmented hyaline cartilage beneath the fovea. **b** (×200) Details of an area near that of Fig. 9b, showing various aspects of phagocytosis of ochronotic fragments

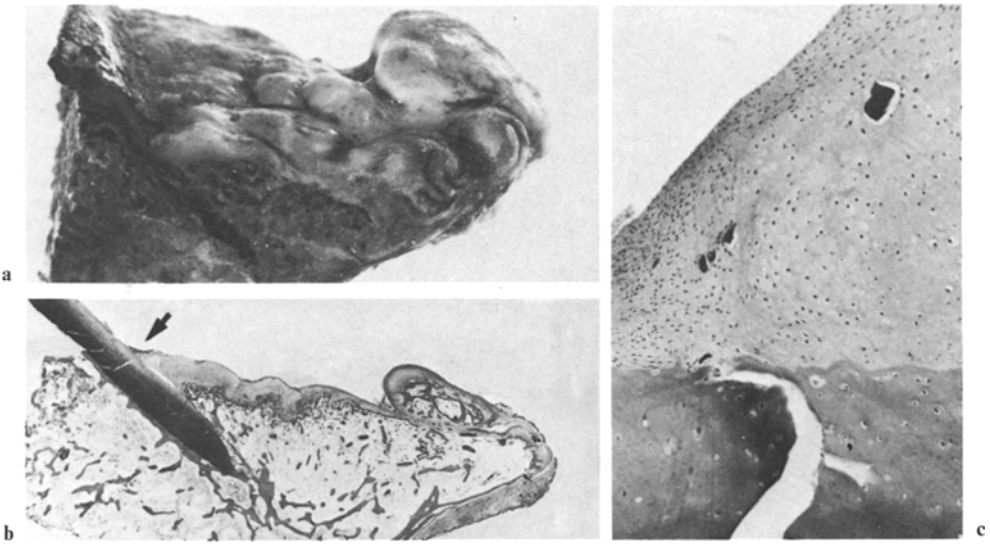

Fig. 11a–c. Specimen VI. Osteophyte with inferior pole of right femoral head. **a** Macroscopic upper frontal view (×3.4). **b** Microscopic view (HE ×4) of longitudinal section of the specimen showing pigmented ochronotic cartilage and non-pigmented newly-formed cartilage covering the osteophyte. **c** Histological detail (HE×60) of the area indicated by the arrow in Fig. 11b. The upper part shows embedded ochronotic fragments in the non-pigmented newly-formed fibrocartilage and the lower the ochronotic preexisting cartilage

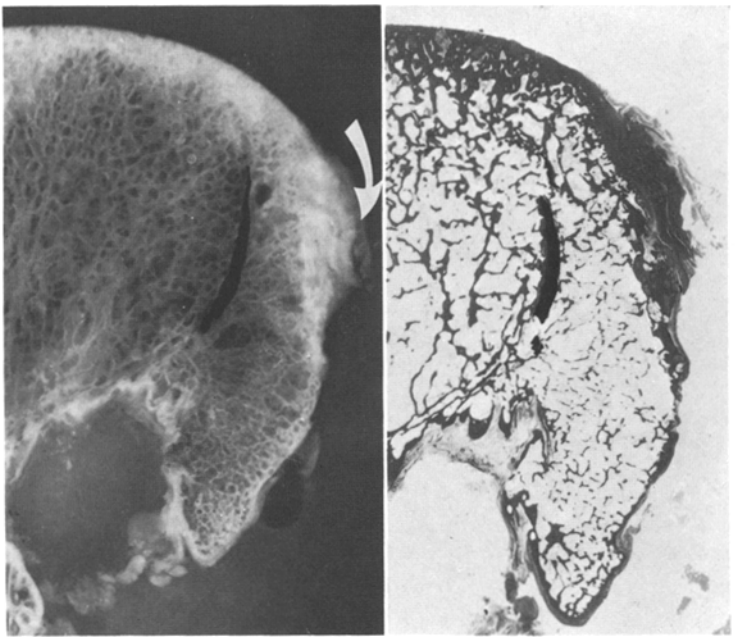

Fig. 12a and b. Specimen VII. Right femoral head; frontal section, medial half. **a** Macroscopic aspect. **b** Microscopic view (van Gieson ×2.3). Preexisting ochronotic cartilage covered by an osteophyte. The eburnated surface of the weight-bearing zone has extended to include the top of the osteophyte. The arrow indicates a stump of the ligament of the head

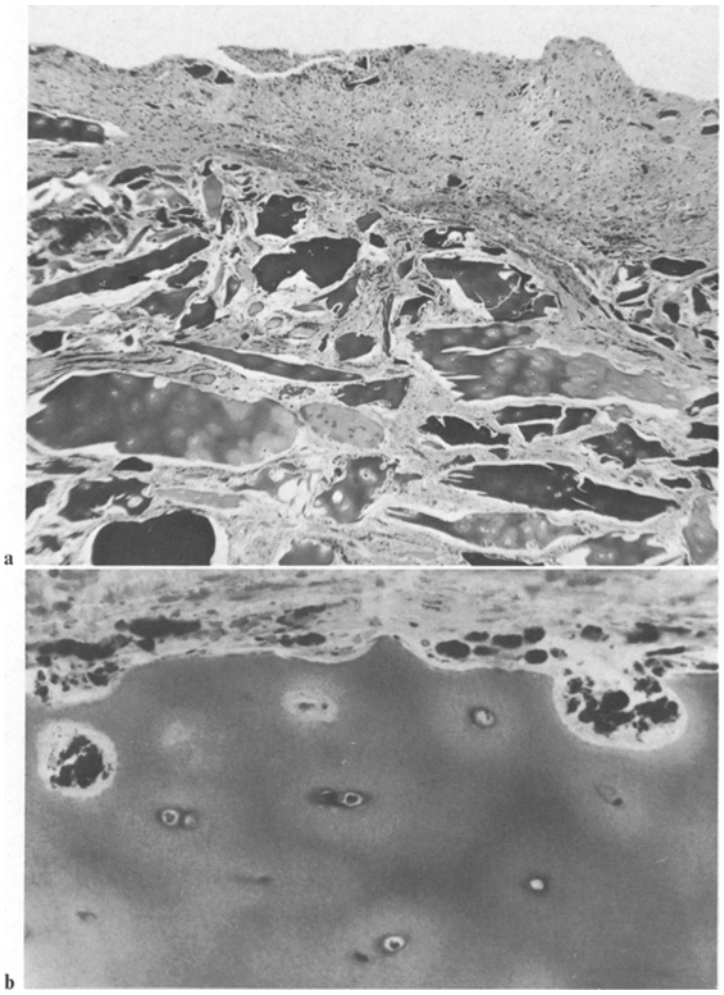

Fig. 13a and b. Specimen VI. Right hip: synovium. **a** (HE × 25) Topographical view showing subintimal fibrosis and embedded ochronotic cartilage fragments. **b** (Nile blue × 200) Detail of eroded surface of an ochronotic cartilage fragment. Pigmented deposits can be seen in the adjacent mononuclear and multinuclear cells but are not present in the chondrocytes

underlying marrow is fibrous and mingled with the bone on which the endosteal remodelling takes place. This remodelling is both resorptive and osteogenic, and produces lamellar as well as woven bone. The fibrous marrow contained large necrotic areas in specimen V and smaller ones in specimens I, II and III. In this remodelled field, small ochronotic cartilaginous fragments were observed, either incorporated into eburnated bone (Figs. 2a, 4a) or in the medullary spaces where they frequently induced phagocytosis; they were particularly numerous in the necrotic zones (Figs. 2a, 4a, 9). Further from the surface, the marrow of the femoral head was fatty but with some scattered macrophages

containing ochronotic pigment. The spongy trabeculae showed signs of old remodelling which was particularly marked in specimens I, II, III and V (Fig. 8).

The non-weight-bearing zone usually showed no classical well-developed osteophyte, but in specimens VI and VII osteophytes were observed overlying a remnant of preexisting ochronotic cartilage (Figs. 11 and 12). On the other specimens, the alteration of the cartilage in the non-weight-bearing zone was demonstrated by what we consider to be the minor equivalents of an osteophyte, i.e. various combinations of the following lesions: a) an evolution toward a still hyaline but unpigmented and Alcian blue stained cartilage (Fig. 5b); b) a dedifferentiation toward a non pigmented fibrocartilaginous layer in which macrophagic cells containing ochronotic pigment were seen (Fig. 6); c) a synovial expanse covering the cartilage and containing embedded ochronotic cartilage fragments (Fig. 10b).

The ligament and acetabular rim tissue was irregularly impregnated with ochronotic pigment. This impregnation can be observed on the stumps of the ligament of the head, particularly at the insertion zones (Figs. 2b, 5a, 8b). It can also be seen on the ligament tissue of the fibrous capsules. The ochronotic bundles tend to become fragmented, inducing a reaction that results in pigmented macrophages.

The synovial membrane contains embedded fragments of unequally pigmented ochronotic cartilage, frequently aggregated into clusters (Figs. 2b, 11, 13a). These fragments sometimes are eroded, have lacunae and are bordered by pigmented macrophages (Fig. 13b). The synovial intima is variably hyperplastic (Fig. 13a). The subintimal layer shows metaplastic newly formed cartilage in specimen VI as well as calcium pyrophosphate dihydrate crystal deposits in specimen VII.

Discussion

By the time osteoarthritis of the hip is diagnosed, there is already a series of well defined changes. Any attempt to reconstruct the sequence of alterations of normal articulation that led to it must therefore combine the systematic analysis of the lesions with a careful evaluation of the clinical and radiological data. This approach requires a precise topographical study based on techniques that allow for an estimation of the relative age of the tissues, e.g., examination of the structures by polarized light and acid polysaccharide staining. Histological analysis of such quasi-"geological" data is quite complex since the lesions often reflect a gradual evolution in which newly formed tissue may have become integrated more or less imperceptibly with preexisting tissue. The problem is even more difficult with alterations due to aging, which are not necessarily those of well-established osteoarthritis but frequently are an indication of similar minor equivalents (Lagier, 1976). Although comparative pathology can provide incipient and intermediary cases for study, its usefulness in solving the problem is limited since animal specimens are rather rarely obtained and since the articular mechanisms of animals are not exactly the same as those of man. As for experimental pathology, it frequently creates artificial conditions that are quite different from those under which the gradual development of human osteoarthritis occurs.

Ochronosis, by providing spontaneous labelling of the preexisting cartilage, offers an exceptionally favorable opportunity to study the anatomopathological evolution leading to osteoarthrotic remodelling. Extrapolation based on observations of the ochronosis specimens in the present study seems completely justified since in fact the data obtained confirmed the observations previously made regarding "degenerative" forms of osteoarthrotic remodelling.

Significance of the Lesions

In each case, the hip showed all three of the essential characteristic components of osteoarthrotic remodelling (Lagier, 1972 and 1976): 1) deterioration of the cartilaginous covering – 2) intrinsic remodelling – 3) extrinsic remodelling. Although, with the exception of specimen VII, this was observed only on femoral heads, the usual mirror image of the acetabulum could be seen in all of the X-rays.

1. Cartilaginous deterioration is the one specific element and is characterized by fragmentation of the cartilage into pieces with sharp edges. The brittleness of the cartilage is due to its impregnation by homongentisic acid in the form of oxidized melanine-like pigment (La Du, 1978). The fragmentation should be distinguished from the "degenerative" alterations of the cartilage which consist of fibrillation with fissures and cell proliferation. Nevertheless, by destroying the protective covering of the underlying bone, the cartilage deterioration process creates the same conditions and results in the same non-specific remodelling as observed in "degenerative" alterations. Both the characteristics of the lesions and extensive clinical data strongly indicate a causal relationship between ochronosis and osteoarthrotic remodelling.

2. The intrinsic bone remodelling had the same characteristics observed in "degenerative" osteoarthrotic remodelling, although no cysts were observed in the present study. It develops in the weight-bearing zone, essentially where the bone has been laid bare, on a surface that may be expanded in the course of the disease (Fig. 12). Sometimes it is observed in deeper parts, but only to a slight extent and is apparent as old remodelling of bone trabeculae (Fig. 8) and pigmented macrophages in medullary spaces. The "breccia" structured bone, abraded on the surface, is the result of osteomedullary remodelling that on balance is principally osteogenic. Remodelling activity is only slight in some cases but in others it is marked and includes considerable necrosis in the marrow spaces (Fig. 9). The incorporation of cartilaginous fragments into the remodelled bone – a well known phenomenon in "degenerative" osteoarthrotic remodelling – is particularly evident, due to their ochronotic pigmentation. These fragments may induce phagocytosis that can sometimes be intense and they are particularly numerous in the necrotic zones (Fig. 9). They might be responsible, at least in part, for the necrosis since it has been reported that phagocytosis can trigger a release of lysosomal enzymes (Dannenberg, 1975) and these are known to cause necrosis. The incorporation of intra-articular

foreign bodies into the remodelled tissue of an eburnated osteoarthrotic zone might well be a general phenomenon since we have already observed it with chromium particles caused by abrasion of a metal-metal prosthesis (Lagier and Bertrand, 1979).

3. The extrinsic remodelling shows the same basic lesions and same qualitative specimen variations as seen in "degenerative" osteoarthrotic remodelling. Only specimen VII shows a well-developed osteophyte; it forms a rim which is more prominent on the inferior-medial part. The fibrocartilage covering the osteophyte is easily distinguishable from the preexisting cartilage, not only because of its different histological structure but also because of the absence of ochronotic pigmentation in this newer tissue. In specimen VI, which had been taken from the same hip eleven years earlier, the covering of the osteophyte has the same characteristics but also shows embedded ochronotic cartilage fragments indicating that the fibrocartilage was the result of metaplasia of a synovial type tissue (Fig. 11c).

Except for a characteristic but very small osteophyte seen in specimen III, the cartilage modification in the non-weight-bearing zone is reflected by similar kinds of dedifferentiation to those seen, to a greater or lesser extent, in other osteoarthritic femoral heads and sometimes in aging. These are a) evolution of the pigmented hyaline cartilage toward a cartilage that is unpigmented but with a remaining tide-mark that can serve as a base of reference (Fig. 5b); the new cartilage is more cellular than the preexisting cartilage and its high polysaccharide content is demonstrated by a diffuse staining with Alcian blue, b) dedifferentiation toward either superficial fibrocartilaginous tissue or a pannus of fibrous synovial type tissue (Figs. 6, 10a).

A careful examination of numerous autopsy and surgical specimens would presumably reveal the existence of a series of intermediary stages between the well-developed osteophytes and what can be considered their minor equivalents both in osteoarthritis and in aging. Nevertheless, an understanding of this evolution is greatly facilitated by the ochronotic pigmentation which can give a clear picture of the relative importance of cartilaginous dedifferentiation and that of synovial expansion in the genesis of osteophytes. The present study also confirms a previous finding that the presence of a pannus is not exclusively indicative of an inflammatory arthropathy with cartilage erosion but is more likely to reflect a process of cartilage adaptation.

The usually modest development of the osteophytes observed in our specimens is in accord with that observed in published X-rays of ochronotic hip arthropathies (Régent et al., 1977; Sitaj, 1973). This is understandable since this arthropathy is the result of a diffuse alteration of the cartilage in a usually congruent articulation. When a sizable osteophyte is observed in cases of ochronosis, it could be presumed to be the result of some special mechanical conditions. However, in the patient from whom specimens VI and VII were taken, no hip dysplasia had been diagnosed and the osteophyte had already been observed before the hip surgery.

Synovial involvement in ochronotic arthropathy of the hip is also an element in the extrinsic remodelling. Unlike alteration of the ligament or fibrous capsule,

in which uneven primary impregnation by ochronotic pigment occurs, the synovial response is only a reaction to the embedded cartilaginous fragments (Fig. 13a). Synovial osteochondromatosis, which is quite frequently observed on X-rays of patients with ochronosis, is only one part of this reaction and is due to bone and cartilage metaplasia (Steiger and Lagier, 1972).

These findings regarding ochronotic hip arthropathy are in accord with those of other authors (Virchow, 1866; Benedek, 1966; O'Brien et al., 1961 and 1963; Searle and Kerr, 1971; Mohr and Richter, 1975; Schumacher and Holdsworth, 1977) as well as with our own previous observations on the knee (Lagier et al., 1971; Lagier, 1973).

Applications to Rheumatology

Although arthropathy of the hip is an infrequently observed peripheral joint affection in ochronosis, it provides an interesting opportunity to study, within a known aetiological context, the osteoarthritic remodelling of an articulation that is of prime importance in rheumatology. In a more general way this may be correlated to some alterations of the hip in other metabolic diseases, for example gout whose lesions are rarely described in this location (Doerr, 1974).

First of all, it allows for a better understanding of the series of non-specific alterations resulting from the deterioration of the cartilaginous covering. It illustrates that even conditions that are quite different in causation, can result in the same range of qualitative modifications observed in the more common types of osteoarthrotic remodelling. Here we can see the frequently osteophytic form with slight remodelling activity (specimen VII) and a highly active and necrotic form (specimen V) which is microscopically similar to that which can be observed in numerous cases radiologically diagnosed as "rapidly destructive hip osteoarthritis" (Abelanet et al., 1974; Lagier et al., 1972; Lequesne and Amouroux, 1970). The fragmentation of the ochronotic cartilage raises the question of whether phagocytosis of foreign particles might be involved in the genesis of the necrosis observed in some cases of osteoarthritic remodelling (Lagier and Bertrand, 1979) and inevitably leads to a questioning of the possible side effects of intra-articular injections.

The extensive weight-bearing zone and the usually modest development of osteophytes observed in ochronotic arthropathy reflect osteoarthrotic remodelling that is the result of a diffuse alteration of the cartilage rather than localized alteration due to a functional defect of the articulation itself. It is understandable, therefore, that the radiological image of this condition is often similar to that of chronic inflammatory rheumatism (Steiger and Lagier, 1972). The radiological differential diagnosis would be made mainly with rheumatoid arthritis, particularly in cases of ochronotic arthropathy with evidence of protrusio acetabuli. A similar differential diagnosis should be made, and for the same reasons, when the shoulder or the knee are involved.

A better understanding of the mechanical functioning of the hip might also be attained by investigating the following questions: a) why, in alcaptonuric

patients, does hip arthropathy occur only in some cases and later in the hip than in other joints? b) Why is the osteophytosis more extensive in some cases of ochronotic hip arthropathy than in others? It should also be noted that the coexistence of chondrocalcinosis and ochronosis observed in specimen VII has been reported elsewhere in the literature but no interpretation of this finding has as yet been attempted.

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