SECTION IV. DISCUSSION

In the available literature we found 32 case-histories reporting the calcification of articular cartilage.

The first report was most probably that presented by Werwath (1928), who found calcification of the menisci and of the hyaline cartilage of the femoral condyles in the left knee with histological evidence in a 45-year-old man; he presumed that a metabolic disturbance was responsible for this condition.

Bruchholz (1929), Israelski and Pollack (1930), and Henrichsen (1932) each reported a similar case.

Wolke (1935) described the results of an investigation of 2,569 knee x rays; he found five cases of calcification of the menisci and hyaline cartilage in the knee joints as well as in the articular cartilage of other joints and the intervertebral disks, and thought that this phenomenon had not previously been observed.

Harmon (1944) reported two cases under the title "degenerative calcification in the articular cartilage", which had been discovered by chance in the course of the radiological examination of a 75-year-old man with intermittent swelling of the left knee, and of a 55-year-old man treated for acute attacks of gout; he suggested that the acute symptoms were due to the calcification of the articular cartilage.

Schrop (1952) reported the calcification of the menisci and articular cartilage of the knee revealed in two women aged 78 and 80 years respectively.

Edwards and Davis (1953) observed "primary asymptomatic calcification of articular cartilage" in a 45-year-old male.

Marziani (1953) reported a case of more extensive calcification affecting articular cartilage in a 28-year-old man under the title "systemic calcium incrustation of articular cartilage".

Bunjé and Cole (1956) reported multiple calcification of articular cartilage in a 31-year-old Jamaican woman who had suffered from intermittent arthralgia for 10 years.

Losada, Cox, Rodriguez, Ronban, and Silva (1957) reported a case of "generalized articular chondrocalcinosis", in which the calcification had become more marked since it had been first noted in 1951 and 1953.

Kelly and Coventry (1957) reported "calcification of articular cartilage associated with calcification of the coxal capsule" in a 57-year-old man, and observed that the fluid obtained from the coxa was of an inflammatory character.

Our first observations of three patients, children of the same parents,* affected with polyarticular chondrocalcinosis were published in 1958; when we pointed out the marked inflammatory superstructure of the condition and first noted its familial incidence (Zitnán and Sit’aj, 1958).

Mühr (1958) reported generalized primary calcification in the articular cartilage of a 33-year-old man, drawing attention to a special constitutional predisposition to the development of this condition.

Another case of polyarticular chondrocalcinosis in a 34-year-old male was reported by Pračke and Mikeš (1959).

Ravault, Lejeune, and Maitrepierre (1959) published their first case of "diffuse articular chondrocalcinosis" in a 51-year-old female. Four such cases were presented by Gauthier (1960). Ravault, Vignon, Lejeune, Maitrepierre, and Gauthier (1961) gave an account of six personal observations (including the five previous French cases); they also referred to the other cases reported so far in the world literature and divided them according to the number of joints affected, into "localized" and "generalized" articular chondrocalcinosis. Two further cases in France of diffuse articular chondrocalcinosis simulating rheumatoid arthritis were published by de Sèze, Hubault, and Kahn (1961), and one by Rubens-Duval, Villaiumey, and Aristoff (1961).

In 1959 and 1960 we published several reports covering what is so far the largest series of cases (Zitnán and Sit’aj, 1960; Zitnán, Sit’aj, Hüttl, Markovic, and Skrovina, 1962). We examined both the familial incidence of articular chondrocalcinosis and the character and development of the arthropathy.

Bywaters had reported in 1958 (published 1959) calcification of articular cartilage in six cases of hyperparathyroidism.

* Cases 3, 4, 5 in Paper I.
Hosking and Clennar (1960) observed calcification of articular cartilage in the shoulders, hips, knees and pubic symphysis with hyperparathyroidism due to parathyroid tumour in a 57-year-old man.

Junet and Schenkel (1961) reported a case of localized articular chondrocalcinosis.

Zvaifler, Reefe, and Black (1962) published an interesting report of articular manifestations in primary hyperparathyroidism in three patients, in whom the x-ray findings differed from those usually encountered in articular chondrocalcinosis. They described the case of a 67-year-old man in whom the pathological picture was identical with that usually seen in polyarticular chondrocalcinosis and in whom parathyroidism could not be demonstrated by laboratory tests or bone biopsy.

Thus, we come to the first pathophysiological problem of articular chondrocalcinosis which arises from a study of almost all the papers cited—that of calcium and phosphate metabolism. Elevated levels of calcaemia are cited only in four reports (Bunjé and Cole, 1956; Losada and others, 1957; Bywaters, 1959; Hosking and Clennar, 1960); of these only the last two mentioned a tumour of the parathyroid gland; phosphataemia was within the range of normal in nearly all these cases. This means that most of the observations on articular chondrocalcinosis reported by us as well as in the world literature gave no evidence of a disturbance of the calcium or phosphorus metabolism. Hence, it follows that the cartilaginous calcification occurring in articular chondrocalcinosis cannot be regarded as metastatic. In our cases as well as in most of those reported by other workers there were, moreover, no destructive processes affecting the bone and no renal insufficiency or hypervitaminosis D.

Most authors discuss the clinical symptoms of articular chondrocalcinosis which take the form of arthralgia or attacks of subacute arthritis. From the pathogenetic point of view, we would describe the clinical symptoms as an inflammatory superstructure of articular chondrocalcinosis, and do not agree with Losada and others (1957) and Bunjé and Cole (1956) who suggest that the calcium deposits in the articular cartilage are caused by recurrent mild arthritis of unknown aetiology. Trauma, which is often discussed in relation to the so-called metatraumatic isolated meniscopathy (Israelski and Pollack, 1930), seems to play no part in the aetiology of articular chondrocalcinosis, because in most cases the calcification occurs at many sites.

In our opinion, the most significant point is the familial incidence of articular chondrocalcinosis. In the literature, familial correlations are suggested only by Schrop (1952), who reported the oligoarticular type in two sisters, and by Ravault and others (1961), who reported the oligoarticular type in a mother and concurrent polyarticular chondrocalcinosis in her daughter. In contrast to this, our own observations present fairly convincing evidence that articular chondrocalcinosis may occur in a greater number of members of one family, so that we regard the condition as rather hereditary than familial, though it is impossible in the present stage of our knowledge to define precisely the type of hereditary transmission.

It has been stated above that the basic criterion which is specific for this disease is radiological evidence of the calcified articular cartilage.

Our genetic studies revealed that the calcification of articular cartilage—which is at first, naturally enough, discrete, and in all cases oligoarticular—precedes the clinical manifestation of arthritis, and is thus temporarily asymptomatic. Early symptoms of calcification could not be diagnosed in the younger members of the family because it first becomes detectable only in adults. We deduce from this either that the cartilaginous calcification represents a late manifestation of an underlying primary process or that the impairment of articular cartilage actually occurs at the adult stage. In the latter case it may depend on those factors which condition the age of sexual maturity and hormone balance, the calcification developing as a consequent and presumably reparative process. As has been shown by histological examination, articular chondrocalcinosis appears to involve a primary metabolic disturbance affecting the replacement of healthy intercellular ground substance in tissues adjacent to the articular cavity, in particular the articular cartilage. We may postulate a hereditary disturbance affecting a segment of the mesenchymal tissue whereby the synovial cavity develops by cavitation in the process of development. This presumed disturbance leads to primary structural alterations, characterized, in the first phase by the development of metaplastic foci associated with the degradation of articular cartilage and the appearance of fibrous structures immediately below the cartilage surface, and in the second phase by the deposition of mineral precipitates in the foci and the development of superficial depressions and cavities.

Though we are not able to elucidate the mechanism of deposition of mineral salts in the affected cartilage, the results of our histochemical investigations have led us to believe that mineral precipitates are not simply deposited in the cavities, but are fixed to the organic substrate of the cartilaginous ground substance. Crystallography has shown the carbon-
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ate apatite to be the principal component of these incrustations, hence we may perceive a certain parallel with the mechanism of physiological ossification—in the sense of a change in the polymerization of chondroitinsulphuric acid. Further, we believe the synovial fluid to be the carrier of the mineral salts which are so deposited, the direct participation of vessels in this degenerative process being out of the question because the process first begins on the cartilage surface.

X-ray examination of our series of cases shows that the mineralization tends to increase, both by spreading and by thickening. It has to attain a certain stage before the disease manifests itself clinically, and causes arthritic episodes, which we consider to be due to the irritant action of the mineral deposits. The humoral activity associated with the arthritic episodes and their liability to spontaneous remission support the non-specific character of the arthritic inflammation. The accompanying changes in the synovial fluid, which is produced in excess (particularly in the knees) with marked inflammation, are characteristic.

Concurrently with the impairment of articular cartilage and with the associated mineralization process there develop conditions favourable to the development of osteo-arthritis even in joints subject to normal use. Hence, it is not surprising that the degenerative alterations in the bone and cartilage appear extremely early; the direct relationship of the osteo-arthritis to the degree of calcification and the functional burden of affected joints is clearly evident. The slow progress of the hyperplastic degenerative alterations is accompanied by a concurrent loss of the “calcified” cartilage, so that after some years the osteo-arthritic alterations predominate. At this stage the arthritic episodes lose their inflammatory character and the joint reacts by exudation of a degenerative nature.

The arthropathy is more progressive if the disease appears early (i.e. in the third decade of life) and thus the polyarticular type develops with marked inflammation. If the onset occurs at a more advanced age (i.e. in the fifth or sixth decade), the disease will assume a more stationary character, will be confined to fibrous cartilage, and will lead to a clinically indistinct and latent oligoarticular type of chondrocalcinosis.

SECTION V. SUMMARY

I. A series of 27 patients with multiple calcification of the hyaline and fibrous cartilages of the joints and intervertebral disks followed for up to 7 years is the basis for a nosographical analysis of this little-known arthropathy.

The disease, called articular chondrocalcinosis, has a familial incidence, affects both sexes, and manifests itself clinically in the third decade of life. It is characterized by the development of arthritic episodes lasting 2 to 4 weeks, which occur at irregular intervals and are accompanied by general malaise and non-specific serum protein changes.

The multiple calcification of superficial layers of articular cartilage, as seen radiologically, is pathognomonic. The calcification has a slow but progressive course and affects successively more and more joints. The chondrocalcinosis may be defined as oligoarticular or polyarticular according to the number of joints affected.

After some years generalized osteo-arthritis develops, and this progresses concurrently with a reduction in the x-ray signs of articular calcification and a lessening of the inflammation.

The oligoarticular type of chondrocalcinosis with onset after the fifth decade, usually remains stationary radiologically, being in most cases clinically latent and mild.

In the differential diagnosis, attacks of rheumatic fever, palindromic rheumatism, atypical rheumatoid arthritis, isolated calcification of the menisci, and conditions associated with calcification of the fibrous cartilages should be taken into consideration.

Therapy can be only symptomatic.

II. Articular chondrocalcinosis is hereditary rather than familial, as is shown by the genetic analysis of five family trees with 21 affected members.

In the present state of our knowledge it is impossible to define precisely the type of hereditary transmission. Point mutation seems to be involved.

III. A pathophysiological study has been based on data describing the metabolism of calcium, phosphorus, free amino-acids, and synovial fluid, histological and histochemical examination of the calcified cartilage, crystallographic analysis of incrustations, and particularly by the genetic analysis.