Is Paget's Disease of Bone a Viral Infection?

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Since 1973, our electron microscope studies of biopsies from patients with Paget's bone disease have consistently revealed characteristic nuclear inclusions in osteoclasts [5-7]. To date, the examination of 61 biopsies from 32 patients before and after treatment has demonstrated the persistence and the specificity of the inclusion bodies. By using a goniometric tilting stage together with optical analysis of the electron micrographs we have elucidated some of the physical aspects of the structure of these nuclear inclusions [2]. Comparison of our observations with those in certain viral disorders leads us to question whether Paget's disease of bone might also be associated with objects of a viral nature.

Material and Methods

Sixty-one iliac crest biopsies were taken from 32 patients before and after treatment for Paget's disease of bone. Undecalcified fragments of bone tissue were fixed at 4° in 4.25% glutaraldehyde with a phosphate buffer at pH 7.2. Post-fixation was carried out in 2% osmic acid. After dehydration and passage of propylene oxide, the fragments were embedded in epon. Thin sections, cut with diamond knives, were stained with uranyl acetate and lead citrate according to Reynolds.

Results

The examinations of biopsies from patients with Paget's bone disease shows that almost all the osteoclasts observed contain at least one nucleus with characteristic inclusions easily distinguishable from the surrounding nuclear material. These

inclusions consist mainly of loosely organized bundles of "micro-cylinders" about 15 nm in diameter (Fig. 1).

In some cases the micro-cylinders are seen in close-packed paracrystalline arrays with an interspace of about 15 nm (Fig. 2). In transverse sections the micro-cylinders appear to have electron-transparent cores of about 5 nm in diameter, and in longitudinal sections, a 5 nm light and dark periodicity is visible. Neighbouring micro-cylinders appear to be associated by cross-linkages with a similar periodicity. The orientation of the striations indicates a possible helicoidal arrangement of the individual micro-cylinders (Fig. 3).

Similar micro-cylinders are also found in the cytoplasm of the osteoclasts though apparently much less organized than in the nuclei. In a few cases we have observed images suggesting the passage of large bundles of micro-cylinders across gaps in the nuclear membrane into the cytoplasm.

Discussion

The presence of nuclear inclusions in osteoclasts from patients with Paget's bone disease has been recently confirmed by other workers [1, 8]. There is thus little doubt as to the specificity of the inclusions with respect not only to the pathological context but also to the particular type of bone cell in which they are found.

Our observations suggest that current treatment of Paget's bone disease dose not modify the structure of the inclusions. Bone resorption is, however, demonstrably reduced and this may be attributed to a decrease in the number of osteoclasts associated with a lower rate of activity.

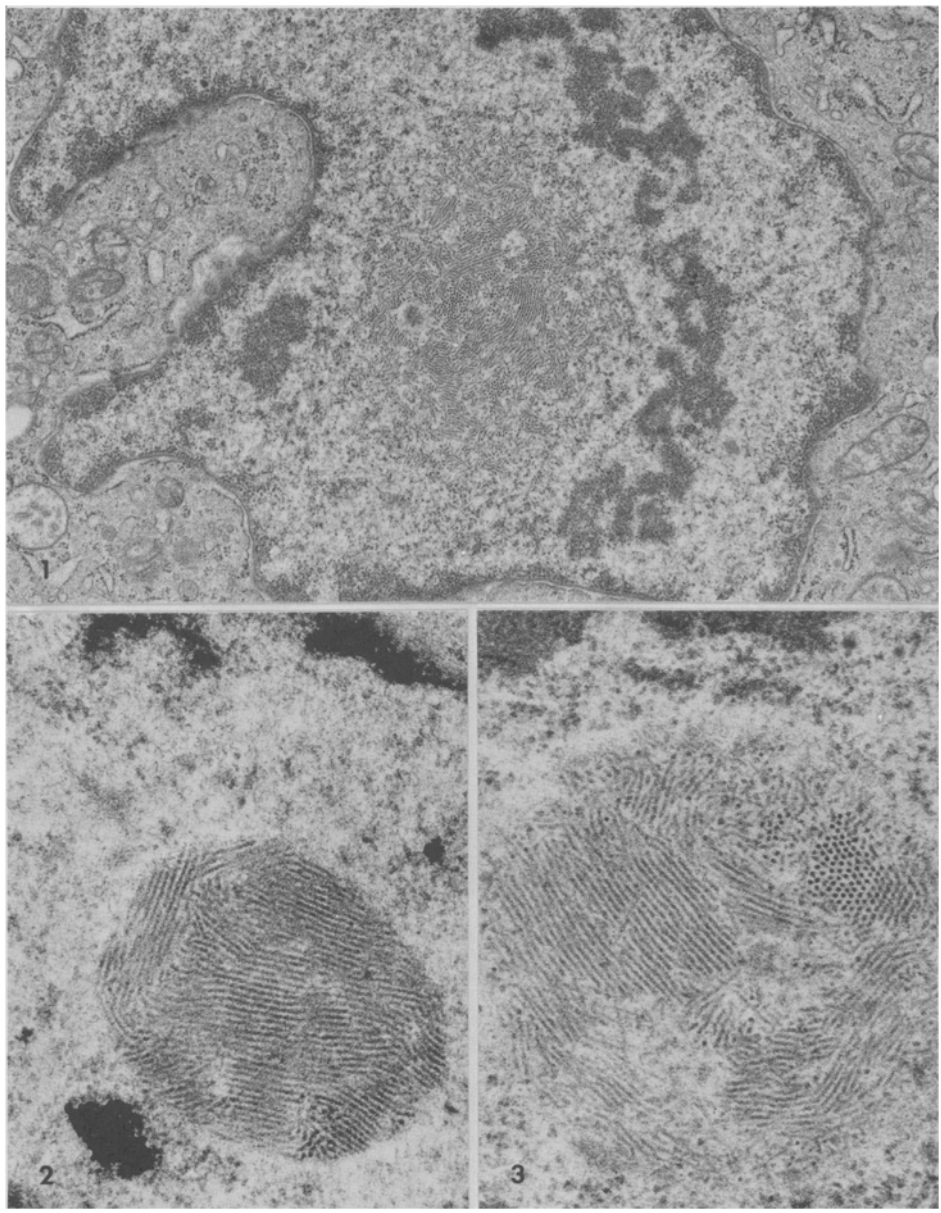
There is a striking morphological resemblance between the inclusions observed in Paget's bone disease and those seen in certain multifocal slow-virus diseases such as subacute sclerosing panencephalitis [3, 4]. A similar comparison can be established with the inclusions described in giant cell tumors of bone [9]. Such tumors are known to turn up as occasional complications of Paget's bone disease, and it would be most interesting to examine bone samples under such conditions.

These analogies suggest a viral agent in Paget's bone disease, but morphological evidence in itself is not conclusive. Current efforts with immunological techniques are expected to give some indication of the etiology of Paget's bone disease.

Fig. 1. Osteoclast nucleus in Paget's bone disease showing characteristic inclusion body; 15 nm diameter micro-cylinders are loosely arranged in bundles seen in oblique and transverse sections, × 16,000

Fig. 2. Inclusion made up of micro-cylinders in close-packed paracrystalline array with an interspace of 15 nm, × 50,000

Fig. 3. Micro-cylinders with 5 nm light and dark longitudinal periodicity; the orientation of the striations suggests a heliciodal organization of the individual micro-cylinders, × 45,000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Acknowledgements

This work was supported by the French Medical Research Foundation. We thank Miss A. Le Patezour and Mr. R. Filmon for skilful technical assistance.

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