LIGHT AND ELECTRON MICROSCOPE STUDIES IN CARRAGHEENIN, ADJUVANT, AND TUBERCULIN-INDUCED ARTHRITIS*

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The classical descriptions of the pathology of rheumatoid arthritis have largely come from autopsy studies in far advanced disease. The frequent use of surgery in recent years has stimulated much interest in the synovial changes by providing material from the earliest proliferative stages. Features previously unrecognized, such as a "distinctive" synovial giant cell, have been described in sero-positive rheumatoid disease (Grimley and Sokoloff, 1966), whilst rarely mentioned deposits of iron in the joints have been shown to be an almost constant finding (Muirden and Senator, 1968). Access to biopsy material has permitted the immediate fixation necessary for electron microscopic examination. Barland, Novikoff, and Hamerman (1964) first described the presence of large cytoplasmic granules or lysosomes in the A type lining cells. Our own studies have emphasized the frequency of ferritin deposits in these cells and a complex cytoplasmic body containing ferritin which seemed characteristic of the material examined has been described (Muirden, 1966).

It has often been stated, however, that unlike the rheumatoid nodule the pathological changes in the synovium in rheumatoid arthritis cannot be considered specific for the disease (Collins, 1949). In this report it will be shown that this remains true. The "distinctive" synovial giant cell, the iron deposits, the distribution of iron within the cell, the lysosomal enlargement, and the "characteristic" lysosome containing ferritin can all be found in forms of experimental arthritis in animals. This applies to the arthritis induced by the mucopolysaccharide carrageenin, which produces its effect by chemical irritation, as well as to the adjuvant and tuberculin-induced arthritis which involve immunological mechanisms.

Material and Methods

(1) Carrageenin Arthritis in Rabbits

The right knee was injected with 0.8 ml. of a 1 per cent. solution of carrageenin in the manner described by Gardner (1960). The left knee received normal saline. Once or twice weekly injections were given for 5 to 6 weeks and the rabbits were then killed. The synovium was divided for histological and electron microscopical use. Light microscope sections were stained with haematoxylin and eosin (H and E) and for iron by the Prussian blue method. The tissue for electron microscopy was fixed either in 1 per cent. osmium tetroxide in veronal buffer or in phosphate buffered formaldehyde (pH 7.2 to 7.4). Staining took place in the dehydration phase with 1 per cent. phosphotungstic acid. After orientation, thin sections were examined in a Hitachi 11A electron microscope.

(2) Adjuvant Arthritis in Rats

Freund's adjuvant was injected intradermally into the tail, or into the skin of the back, or into both sites. The rats who developed a polyarthritis were killed approximately 21 days after inoculation. Synovium was dissected from the hind paws and fixed for electron microscopy. The affected carpal and tarsal areas were removed and after decalcification prepared for light microscopy.

(3) Tuberculin-induced Arthritis in Guinea-pigs

Guinea-pigs were inoculated with 0.1 ml. of the non-virulent BCG strain of mycobacteria containing 1×10^6 organisms. 6 weeks later a Mantoux test was performed and a 1 cm. reaction to 0.1 ml. 1:1000 old tuberculin injected intradermally was considered positive in the presence of a negative control. The knee joints of Mantoux-positive animal were then injected with 0.2 ml. 1:1,000 old tuberculin under ether anaesthesia. Animals were killed 2, 6, 12, 24, and 48 hours later. Control (Mantoux-negative) guinea-pigs also received intra-articular injections and were examined at similar time intervals. The synovial membrane was removed from the knee and prepared for light and electron microscopy.

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Results

(1) Carrageenin Arthritis in Rabbits

The right knee became swollen after four or five injections and when opened showed an excess of turbid fluid and thickening of the synovial membrane. The light microscopical features have been outlined by Gardner (1960), who described villous proliferation, lymphocyte infiltration, surface fibrin deposits, erosion of bone, and cartilage replacement by pannus. In addition, we have noted a patchy infiltration with plasma cells and neutrophils, often in considerable numbers (Fig. 1). The stroma contained two forms of multinuclear giant cells. The commonest was a "foreign body giant cell" with nuclei concentrated towards one pole of the cell. This could be distinguished from a somewhat smaller cell with peripherally placed nuclei (Fig. 2). The latter have previously been described as distinctive of sero-positive rheumatoid arthritis (Grimley and Sokoloff, 1966). The other previously unreported feature was the presence of haemosiderin granules in occasional stromal macrophages. The lining cells rarely contained iron and the extensive deep deposits of iron seen in rheumatoid arthritis were absent (Muirden

Fig. 1.—Carrageenin arthritis: cellular infiltrate consists of neutrophils, lymphocytes, and many plasma cells. Haematoxylin and eosin. $\times 560$.

Fig. 2.—Carrageenin arthritis: arrow indicates a giant cell with peripherally-placed nuclei more typical of rheumatoid arthritis. Haematoxylin and eosin. $\times 625$.

and Senator, 1968). A comparison between the synovial features of this disease, Reiter's syndrome, and the three forms of experimental arthritis appears in the Table.

TABLE
LIGHT MICROSCOPE FEATURES OF THE SYNOVIAL MEMBRANE IN EXPERIMENTAL ARTHRITIS COMPARED WITH RHEUMATOID ARTHRITIS AND REITER'S SYNDROME

Features	Experimental Arthritis			Rheumatoid Arthritis	Reiter's Syndrome
	Carrageenin	Adjuvant	Tuberculin		
Villous hypertrophy	++	+	+	++	+
Erosions and pannus	+	+	O	++	+
Lymphocyte follicles	+	+	+	++	+
Plasma cells	+	+	+	++	+
Neutrophils	++	+	+	+	++
Giant cells (foreign body)	+	±	+	+	±
Giant cells (rheumatoid type)	+	±	O	+	O
Iron deposits	+	+	+	++	+

O = absent; ± = rarely present; + = present; ++ = common or extensive

The left knee injected with control saline showed few changes from the normal synovium. Some of the stromal macrophages contained iron but this was of minor degree by comparison with the carrageenin joints. Needle trauma causing bleeding into the synovial cavity could have accounted for this.

Electron Microscopy.—There was an increase in size and number of both A and B type lining cells, with the B cells predominating. The A cells were identical with the stromal macrophages, which contained large and varied inclusions. Some of the inclusions appeared to derive from ingested neutrophils (Fig. 3) and an occasional fortuitous section showed the actual phagocytosis of the neutrophil by the macrophage. Other inclusions were uniformly dense or consisted of myelin figures, and some presumably phagocytosed material could be recognized as collagen fibres (Fig. 4). Tiny dense granules with the molecular dimensions of ferritin were concentrated into vacuoles or scattered in the cytoplasm of occasional macrophages. The organization of ferritin into characteristic lysosomes described in rheumatoid arthritis was not seen (see below). Autophagic vacuoles containing degenerate mitochondria were included in the varied lysosomes seen in these cells. The type B cells contained smaller and less numerous lysosomes and otherwise appeared normal.

The neutrophils seen in the stroma showed degenerative changes in their granules and some of the

plasma cells contained dilated cisternae. Fibrin-like material surrounded many of the surface cells, but the extracellular spaces otherwise contained collagen and finely granular material. The capillaries in the stroma appeared normal.

The saline-injected control joints showed no definite abnormalities.

(2) Adjuvant Arthritis in Rats

The articular and extra-articular features of this disease have been reviewed by Pearson (1963). Fig. 5 shows the synovial and periosteal proliferation and pannus formation in a tarsal joint. Other light microscopical features are summarized in the Table. Giant cells were rarely seen but when present included the form shown in Fig. 2. Variable amounts of haemosiderin occurred in the subintimal layers and Prussian blue stains confirmed the presence of iron within macrophages (Fig. 6, overleaf). This could be considered a significant finding as, unlike the other examples, there was no possibility of needle trauma causing joint haemorrhage in this type of experimental arthritis.

Fig. 3.—Carrageenin arthritis, electron micrograph: large macrophage on left contains an inclusion which is a phagocytosed neutrophil remnant (arrow). The neutrophil (PM) shows degenerative changes. Osmium fixation. $\times 12,500$.

Fig. 4.—Carrageenin arthritis, electron micrograph: membrane-bounded areas in this synovial cell contain myelin figures, granular material which is probably ferritin (F), and fibrous material (C) which is identical in appearance with the extracellular collagen fibres. Similar fibres are shown on cross section (arrows). Osmium fixation. $\times 35,000$.

Fig. 5.—Adjuvant arthritis, tarsal joint of rat: periosteum and synovium are proliferated and pannus formation has commenced. Haematoxylin and eosin. $\times 140$.

Fig. 6.—Adjuvant arthritis, tarsal joint of rat: black deposits beneath the proliferated lining layer represent iron within macrophages. Prussian blue. $\times 560$.

Fig. 7.—Adjuvant arthritis, electron micrograph: cytoplasm and nucleus (N) of a synovial cell containing a prominent golgi zone (G), some endoplasmic reticulum, small mitochondria, and many small dense bodies. Similar structures were seen but were much less frequent in control joints. Osmium fixation. $\times 45,000$.

Electron Microscopy.—The intimal proliferation consisted of both A and B type cells and also large cells with the combined features of endoplasmic reticulum, a Golgi apparatus, and dense bodies. Many of the dense bodies or lysosomes were of an unusual type (Fig. 7), containing uniform dense structures approximately 0.06μ in diameter, but

some with larger dimensions. At first the possibility that these could represent self-replicating organisms was considered, but the presence of identical if less numerous structures in synovial cells in control animals makes this unlikely. Ferritin was seen only in the inoculated rats and Fig. 8 (overleaf) shows an example of the lysosomal organization of ferritin in

Fig. 8.—Adjuvant arthritis, electron micrograph: cytoplasmic dense body is seen with a concentration of small granules having the dimensions of ferritin. Osmium fixation. $\times 82,000$.

Fig. 9.—Tuberculin-induced arthritis: lumen to the right; synovial lining cells show enlargement and mild proliferation. Stroma is infiltrated with lymphocytes. Haematoxylin and eosin. $\times 560$.

the form identical with what has been commonly seen in rheumatoid synovial cells (Muirden, 1966). Some of the synovial cells contained lipid droplets or myelin figures indicating degeneration changes.

Neutrophil scattered throughout the synovium also showed degenerative changes, and identifiable remnants of neutrophils were present within synovial macrophages.

Fig. 10.—Tuberculin-induced arthritis, electron micrograph: synovial lining cells surrounded with unbanding fibrin-like material. Similar material is seen within a vacuole (arrow). Intracellular filaments well developed in cell to the right. Lumen to the left. Formaldehyde fixation. $\times 22,500$.

(3) Tuberculin-induced Arthritis in Guinea-pigs

Mantoux-positive animals showed light microscopical changes 12 hours after injection consisting of enlargement of surface cells, vascular dilation, and extravasation of erythrocytes and lymphocytes. At 24 hours synovial surface cell proliferation was established and the stroma contained increased numbers of histiocytes, fibroblasts, and lymphocytes (Fig. 9, p. 397).

Plasma cells and neutrophils were rarely seen but small foreign body giant cells were not uncommon. The "rheumatoid" giant cell was not seen. The synovial proliferation and infiltration with lymphocyte follicles was intensified at 48 hours. The stromal blood vessels were often surrounded by aggregates of lymphocytes and many were narrowed by intimal proliferation. Prussian blue stains showed scattered deposits of iron within stromal macrophages.

Mantoux-negative guinea-pigs acted as controls. At 24 hours there was little change from normal but at 48 hours moderate proliferation of surface cells and stromal macrophages had occurred. There was also a mild lymphocytic infiltration and some minor

deposits of iron. The changes at this stage approached the intensity of the reaction at 24 hours in Mantoux-positive animals.

Electron Microscopy.—In Mantoux-positive animals the ultra-structural changes at 24 and 48 hours after the initiating injection were much the same. Synovial surface proliferation consisted predominantly of the B type cells but there were also increased numbers of enlarged A type cells. Fibrin-like material was prominent around the surface cells (Fig. 10) and some of this could be seen within the vacuoles of the macrophages. As with the carrageenin arthritis, the lysosomes were enlarged and pleomorphic and contained phagocytosed neutrophil remnants, myelin figures, and ferritin. The organization of ferritin in the lysosome as shown in Fig. 8 was not uncommon. Sometimes ferritin molecules were densely clumped together in membrane-bounded structures corresponding with haemosiderin granules seen on light microscopy.

Synovial tissue from Mantoux-negative animals at equivalent times showed similar but much less intense changes. The lysosome containing ferritin was not identified.

Discussion

The presence of focal collections of lymphocytes and plasma cells in the synovium in rheumatoid arthritis suggests that immunological factors are important in the pathogenesis of the synovial lesion. Fluorescent stains demonstrating immunoglobulins within the cytoplasm of the plasma cells adds support to this (Mellors, Nowoslawski, Korngold, and Sengson, 1961). We have found, however, that a synovial infiltration of lymphocytes and plasma cells is prominent in the arthritis induced by the mucopolysaccharide carrageenin. The reactivity of this substance appears to depend on chemical irritation as it is not known to be antigenic (Gardner, 1960). It is possible that a tissue antigen is released by the chronic irritation and inflammation and this then incites a local immune response. Phillips, Kaklamanis, and Glynn (1966) have established that experimental animals can be immunized with their own inflammatory exudate and a chronic arthritis can be induced by intra-articular injections of this material. Although plasma cells were common in carrageenin arthritis they were notably absent in the hypersensitivity reaction induced by intra-articular tuberculin in sensitized guinea-pigs. The prominent infiltrating cell here was the lymphocyte and the proliferative changes were much less conspicuous. This probably was related to the shorter duration of the disease process: 48 hours compared with 5 to 6 weeks for the carrageenin arthritis. Kulka, Bocking, Ropes, and Bauer (1955) have shown that plasma cells are often absent in early rheumatoid lesions.

Lymphoid follicles were not conspicuous in synovial villi in adjuvant arthritis but the inflammatory cell infiltrate did consist of lymphocytes and plasma cells as well as neutrophils. Periosteal and tendon involvement were constant features. The neutrophil and periosteal response suggests a similarity with Reiter's syndrome (see Table) which also shares extra-articular manifestations in the skin, eyes, and genito-urinary systems. Most of the evidence suggests that adjuvant arthritis is a form of delayed hypersensitivity and that the antigen is the Wax D fraction of the tubercle bacillus (Pearson, 1963). Recent work has reopened the possible role of infection by showing that the antiviral agent Statalon has a protective effect on adjuvant arthritis without affecting tuberculin sensitivity (Kapusta and Mendelson, 1967). The host reaction to adjuvant might upset a commensal balance between the tissues and a "latent or masked" virus which then becomes involved in the pathogenesis of the experimental disease. Our studies, however, provide no morphological evidence for the presence of virus or

Bedsonia organisms in the synovial tissues in adjuvant arthritis.

Grimley and Sokoloff (1966) have recently described a special type of giant cell in the synovium in sero-positive rheumatoid arthritis. The peripheral distribution of nuclei distinguishes these cells from multinuclear plasma cells or foreign body giant cells which were also seen occasionally in the rheumatoid synovium. The finding of similar giant cells in carrageenin arthritis suggests that they are not specific for rheumatoid arthritis. The larger foreign body giant cell was also seen, usually in association with particular debris presumably too large to be phagocytosed by a single macrophage.

One electron microscopic feature common to all three forms of experimental arthritis was the occurrence of neutrophil remnants within synovial macrophages. Similar inclusions are frequently seen in Reiter's syndrome (Norton, Lewis and Ziff, 1966), but are found only rarely in rheumatoid synovia (Norton and Ziff, 1966). More recently, Schumacher (1968) reported widespread phagocytosis of neutrophils in the synovitis of pseudo-gout and suggested that this occurred whenever large numbers of cells were emigrating through the proliferated synovium. In our own material inclusions were very prominent in carrageenin arthritis where neutrophils made up a large proportion of the cell infiltrate. The rarity of such inclusions in rheumatoid arthritis seems to be related to the patchy presence of neutrophils within the synovium.

As well as neutrophil remnants the macrophages were noted to contain fibrin-like material and on rare occasions collagen fibres. The collagen was always membrane-bounded and could readily be distinguished from intracytoplasmic fine filaments commonly seen in synovial cells. It is possible that fibrin and collagen occurred in invaginations of the cell membrane rather than being truly enclosed within cell vacuoles. But synovial cells are not typically invaginated to the degree that would be necessary to explain the depth from the cell surface of these fibres. Intracellular collagen fibres have previously been reported in pathological states including certain types of inflammation (Welsh and Meyer, 1967).

Far more frequent than fibrin and collagen was the presence of haemosiderin and ferritin within the synovial macrophages. We recently have shown that iron deposits are consistently present in rheumatoid synovia (Muirden and Senator, 1968), and we have suggested that the continued oozing of blood from the vascular granulation tissue is responsible. Iron deposits were seen in all three forms of experimental arthritis but also in some of the control joints where saline had been injected on several occasions.

Haemorrhage induced by needle trauma was evidently a factor, but more extensive deposits of iron were seen in the inflamed joints and in the synovium in adjuvant arthritis where the effect of needle trauma could be excluded.

The similar distribution of ferritin within the cell cytoplasm was also of interest. In rheumatoid arthritis ferritin is frequently seen within a characteristic lysosomal body (Muirden, 1966). The non-specific nature of this structure seems confirmed by our findings in two forms of experimental arthritis, although an intensive search in carrageenin arthritis revealed ferritin within cells and many complex lysosomes but none with the features shown in Fig. 8. Ferritin has been described in association with histochemically proven lysosomes in the liver, spleen, and kidney (Novokoff, 1961; Ericsson, Trump, and Weibel, 1965). We have not attempted to prove with acid phosphatase localization that the cytoplasmic dense bodies are lysosomes, but their appearance is strongly in favour of this supposition. Their size, number, and complex appearance contrast with the smaller dense bodies of the normal synovium.

If the macrophage synovial cells provide the most striking morphological changes in experimental arthritis, the B type cells are also involved. There is an increase in size and population and in fact the B cells and intermediate forms predominate over the A type macrophage cells in the synovial proliferation. This has also been found in studies of rheumatoid synovia by Wyllie, Haust, and More (1966) and by Ghadially and Roy (1967). The stimulus to A cell hypertrophy and lysosomal enlargement would appear to be excessive phagocytosis, whilst the most likely reason for B cell increase would be a stimulus to form more protein. The protein could be collagen, or a part of the finely granular material found around the surface cells, or a protein contribution to the synovial fluid. The cytoplasm of the B cells

show no constant abnormalities, but it is possible that they are producing an altered protein under the stimulus of the agent provoking the arthritis. The protein could act as an antigen responsible for the lymphocyte and plasma cell infiltration.

Summary

The histology and ultrastructure of three forms of experimental arthritis have been described. The synovial changes were compared with rheumatoid arthritis and Reiter's syndrome. Focal collections of lymphocytes and a plasma cell infiltration were seen in carrageenin-induced arthritis which is produced by chemical irritation. It is possible that the initial inflammation releases a tissue antigen which then produces a local immune response. Other features in common with rheumatoid arthritis were a distinctive synovial giant cell, deposits of iron, bony erosions, and pannus formation. Additional features present in adjuvant arthritis can be found in Reiter's syndrome. Plasma cells were not prominent in the arthritis induced by intra-articular tuberculin in sensitized guinea-pigs.

Electron microscopy showed proliferation of both A and B type synovial cells. The macrophages contained enlarged complex lysosomes, and phagocytosed material included neutrophils, ferritin, fibrin-like material, and probably collagen. A characteristic lysosome containing ferritin commonly seen in rheumatoid synovia was demonstrated in two forms of experimental arthritis. Micro-organisms could not be identified in the synovial tissue in adjuvant arthritis.

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L'étude au microscope optique et électronique de l'arthrite expérimentale

RÉSUMÉ

L'histologie et l'ultrastructure de trois formes d'arthrite expérimentale ont été décrites. Les changements synoviaux ont été comparés à ceux de l'arthrite rhumatoïde et du syndrome de Reiter. La rassemblement focal des lymphocytes et l'infiltration des cellules du plasma ont été vus dans l'arthrite provoquée par le carrageen qui est produite par irritation chimique. Il est possible que l'inflammation initiale libère un antigène de tissu qui produit alors une action immunologique locale. D'autres signes en commun avec l'arthrite rhumatoïde étaient une cellule géante synoviale distinctive, des dépôts de fer, des érosions osseuses et une formation de pannus. D'autres caractères additionnels présents dans l'arthrite adjuvante peuvent être vus dans le syndrome de Reiter. Les plasmocytes n'étaient pas en évidence dans l'arthrite causée par la tuberculine intra-articulaire chez les cobayes sensibilisés.

Le microscope électronique montrait une prolifération des deux types A et B des cellules synoviales. Les macrophages contenaient des lysosomes complexes dilatés, et la matière phagocytosée comprenait des neutrophiles, de la ferritine, une substance ressemblant à la fibrine et probablement du collagène. Un lysosome caractéristique contenant de la ferritine vu souvent dans la synovie rhumatoïde a été démontré dans deux formes d'arthrite expérimentale. Les micro-organismes n'avaient pu être identifiés dans le tissu synovial dans les cas d'arthrite à adjuvant.

Estudios con microscopio optico y electronico en de la artritis experimental

SUMARIO

Se han descrito la histología y la ultraestructura de tres formas de poliartitis experimental. Los cambios sinoviales fueron comparados con la poliartitis reumatoide y el síndrome de Reiter. Colecciones focales de linfocitos y una infiltración de células plasmáticas fueron observadas en poliartitis causada por carrageen (musgo de Irlanda), la cual es producida por irritación química. Es probable que la inflamación inicial deje en libertad un antígeno de tejido que luego produce una reacción inmunológica local. Otras características comunes a la poliartitis reumatoide eran una célula gigante sinovial distintiva, depósitos de hierro, erosiones óseas y formación de pannus. Otros síntomas adicionales presentes en la poliartitis adyuvante pueden ser hallados en el síndrome de Reiter. Las células plasmáticas no eran prominentes en la poliartitis causada por tuberculina intraarticular en conejillos de Indias sensibilizados.

La microscopia electrónica reveló proliferación de los tipos A y B de células sinoviales. Los macrófagos contenían lisosomas complejos agrandados y el material fagolítico abarcaba neutrófilos, ferritina, material parecido a la fibrina y probablemente colágeno. Un lisosoma característico que contenía ferritina, observado comúnmente en la sinovia reumatoide, se puso de manifiesto en dos formas de poliartitis experimental. Los micro-organismos no pudieron ser identificados en el tejido sinovial de la poliartitis adyuvante.