Etiological Factors, Stages, and the Role of the Foreign Body in Foreign Body Tumorigenesis: A Review

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SUMMARY

Attempts were made to analyze the process of foreign body (FB) tumorigenesis and to identify etiologically significant factors by correlating information in the literature and recent experimental data from our laboratory. It appears that the process of FB tumorigenesis is dependent on a sequence of specific conditions as expressed by the following criteria: (a) cellular proliferation and tissue infiltration during acute FB reaction; (b) fibrosis of the tissue capsule surrounding the FB; (c) quiescence of the tissue reaction, i.e., dormancy and phagocytic inactivity of FB-attached macrophages; and (d) availability of a FB surface for direct contact with clonal preneoplastic cells. There is no indication that the initial acquisition of neoplastic potential and the determination of specific tumor characteristics are based on direct physical or chemical reaction between cells and the FB. These etiological key events occur presumably in mesenchymal stem cells associated with the microvasculature no later than during the acute stage of FB reaction and certainly long before clonal descendants of these cells are first found in contact with the FB surface. In fact, there is reason to assume that cells with neoplastic determination may be present in normal tissue prior to the introduction of a FB and that the FB would only create the conditions required for stepwise preneoplastic maturation.

INTRODUCTION

Much information has become available in recent years concerning FB tumorigenesis in rats or mice. The early work of Oppenheimer’s group and others, cited by Bischoff and Bryson (3), established the important basic fact that the physical presence and nature of the FB material, not its chemical reactivity, were responsible for tumor development. Many investigators studied the histology of tissue reactions in different animal species in response to FB’s of different sizes, shapes, or surface properties. The results indicated that tumor incidence was strongly influenced by the type and course of the FB reaction (2, 3, 12, 18, 20). The degree of fibrosis in FB encapsulation and a chronic course of FB reaction with low cellular activity were positively correlated with FB tumor incidence. More recently, in the authors’ laboratories, the origin of cells with neoplastic determination was identified and their clonal development was followed up (6, 9, 15). In the present review an attempt is made to correlate these data and observations with the course of the tumorigenic FB reaction as studied histologically and by electron microscopy. It appears that FB tumorigenesis proceeds through several stages, each seemingly providing specific conditions required sequentially for preneoplastic maturation. Various factors can be recognized as being etiologically involved and the role of the FB itself becomes clearer. Not only does the insight gained seem important for future experimentation in FB tumorigenesis but it could also add new perspectives in the exploration and understanding of cancer in general.

Materials and methods referred to in this paper have been described in previous publications (6, 9).

IDENTITY AND CLONAL DEVELOPMENT OF CELLS WITH NEOPLASTIC DETERMINATION

Plastic films (unplasticized vinyl chloride acetate copolymer, 15 x 22 x 0.2 mm) were implanted in CBA/H or CBA/H-T6 mice. After various time periods the implants were excised and cut into 7 x 15-mm segments. These were transferred separately to recipient mice that were fully histocompatible yet distinguishable from the donor mouse on the basis of the T6 chromosomes. Sarcomas of donor origin developed in the recipients up to 2 years later, indicating that preneoplastic cells resided on the FB surface at the time of transfer (6). Tumors that arose from segments of the same original implant were often identical or closely related (“homologous”) with regard to (a) tumor latency, in that neoplastic growth commenced in all recipients at closely spaced points in time (6); (b) specific chromosome aberrations, in terms of number and morphology (6); (c) histopathology, in terms of sarcoma type and degree of anaplasticity (13); and (d) growth characteristics and cell generation times in vivo and in vitro (K. G. Brand, unpublished).

These results led to the following conclusions (6). In the case of homology, tumors must have arisen from cells with the same neoplastic specificity, pointing to their clonal nature. Specific tumor properties must have been predeter-
mined in these clonal cells long before they actually started neoplastic proliferation. In fact, specific clones must have been in existence before implants were cut and segments transferred. The demonstration of such clones implied prior existence of "parent cells" in which the initial event must have taken place, the event that not only created the neoplastic potential but moreover predetermined the specific tumor properties.

Although millions of cells, mainly of the bone marrow-derived macrophage type, are mobilized in experimental tumorigenic FB reaction (7, 14), the number of preneoplastic parent cells was found to be extremely small. By applying the maximum likelihood estimate, it was calculated that in CBA mice the most probable number of preneoplastic parent cells is only 1 in response to a single 7-x 15- x 0.2-mm plastic film and 3 in response to a single 15-x 22- x 0.2-mm implant (11). These values are consistent with direct experimental counts (19). It appears that the key tumorigenic event is a statistical chance event or else that a small constant proportion of the cell population has a primary neoplastic disposition or susceptibility.

Various experimental attempts were undertaken to determine the origin and identity of the preneoplastic parent cells. The most conspicuous participants in FB reaction (i.e., monocytes, macrophages, and fibroblasts) were not considered the likely progenitor cells. Instead, ultrastructural studies of tumor cells implicated a pluripotential mesenchymal cell type possessing morphological characteristics consistent with cell types of the microvasculature (15). The endothelial cell, the smooth muscle cell, and especially the pericyte, all being fixed structural parts of the microvasculature, are given special consideration as probable parent cells.

### Appearance Time and Location of Preneoplastic Cells Relative to the Course of FB Reaction

Modified transfer experiments similar to those described above were carried out with segments of implants and FB-reactive capsule tissue at various times during preneoplastic FB reaction (9).

Upon implantation of the FB and through the 1st few weeks masses of monocytes and macrophage-type cells, variable numbers of polymorphonuclear leukocytes, as well as occasional fibroblasts infiltrate the FB environment (Fig. 1a). Capillary outgrowth is seen to take place as in wound healing. From the 12th day on, the surface of the FB is almost completely covered by a monolayer of macrophage-type cells (Fig. 2a). During this 1st month of FB reaction preneoplastic cells are demonstrable in FB-reactive tissue but not in firm contact with the implant itself (Chart 1) (8, 9).

During the 2nd month following implantation, while the FB reaction shows the criteria of a subacute inflammation with continuing cellular activity, a grossly recognizable thin tissue capsule begins to develop around the FB. Fibroblast-like cells, present on the inner aspect of this capsule, are separated by a fine capillary space from the cell monolayer on the FB surface. Fibroblastic cells become more numerous and collagen fibers appear in the capsule wall, which gradually thickens and consolidates (Fig. 1b). At this time, preneoplastic cells are still not detectable on the FB surface itself. However, they can be demonstrated, in some instances already as clones, in the consolidating capsule and in the loose FB-reactive tissue surrounding the capsule (Chart 1).

During the 3rd and the following months, fibrosis of the capsule with pronounced collagen formation continues until this process becomes stationary between the 4th and the 6th month (Fig. 1c). The macrophage-type cells, which still predominated on the FB surface (Fig. 2b), take on an appearance of inactivity and dormancy, signaled ultrastructurally by a decrease in the number of cellular organelles and the presence of electron-dense cell matrices (Fig. 3) (14). Clonal preneoplastic cells are regularly demonstrated in the capsule tissue and now with increasing probability also on the FB surface itself as a component of the firmly attached cell monolayer (Chart 1). The earliest successful demonstration of preneoplastic cells on the FB surface was accomplished in 1 experiment out of several at 11 weeks.

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### Chart 1. Stages of FB tumorigenesis as based on (a) histological and ultrastructural characteristics of FB-reactive cells and tissue and (b) demonstration of preneoplastic cells with different grades of preneoplastic maturation at specific locations in relation to the FB reaction.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Prominent Morphological Criteria</th>
<th>Location and Tumorogenic Maturation of Preneoplastic Cells</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Early FB reaction, cellular proliferation and infiltration</td>
<td></td>
<td>1 to 2</td>
</tr>
<tr>
<td>II</td>
<td>Fibrosis of FB-reactive tissue capsule</td>
<td>Phagocytic inactivity of FB-attached macrophages</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Chronic quiescent FB reaction, dormancy and phagocytic inactivity of FB-attached macrophages</td>
<td></td>
<td>After 25</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td></td>
<td>After 4</td>
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<tr>
<td>V</td>
<td></td>
<td></td>
<td>5 to &gt;30</td>
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</tbody>
</table>

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*MONTHS POSTIMPLANTATION*

- PC (Premarkneoplastic Parent Cell)
- CC (Maturation stages of preneoplastic clonal cells)
- TC (Tumor Cells)

**FOR FURTHER EXPLANATIONS AND DEFINITIONS SEE TEXT**
postimplantation (8). After that time the success rate increased from about 30% during the 5th month to 70% and then nearly 100% during the 6th and 7th months, respectively.

One procedural step in these experiments appears to be of particular significance beyond mere technical consideration. Demonstration of the preneoplastic cells in capsule tissue by transferring segments to recipients was achieved only when a new piece of FB material was inserted into the capsule segment to replace the original implant. Segments from these same capsules would not lead to tumors when transferred empty during this preneoplastic period (5).

STAGES AND ETIOLOGICAL FACTORS OF FB TUMORIGENESIS

First Stage: Initiation of FB Reaction Resulting in Origination or Activation of Cells with Neoplastic Determination

Experimental Findings. The 1st stage begins with the implantation of the FB and the initiation of the FB reaction. The main characteristics of this stage are the morphological signs of early inflammation as manifested by marked cellular infiltration of the implantation site, predominantly by macrophage-type cells and variable numbers of neutrophils (Figs. 1a and 2a). This appearance of the FB reaction was seen to persist in our experiments for about 1 to 2 months (6, 7, 14).

Within 4 to 8 weeks postimplantation, preneoplastic cells (Chart 1, PC), which are presumably derivatives of the microvasculature, appear in the loose cellular FB-reactive tissue (9). However, preneoplastic cells were never demonstrated during this stage on the FB itself (8, 9), although its surface is covered already within 2 weeks by a cell monolayer mostly of the macrophage type (7). It may be argued that preneoplastic cells nevertheless make transient or very loose contact with the FB at this time. However, this appears unlikely. When cells make contact with the FB surface they generally seem to adhere rather firmly, especially if the FB material is a plastic as in our experiments.

Conclusions and Interpretations. These findings indicate that the preneoplastic cells have acquired their neoplastic determination at a site distant from the FB and independent of direct physical or chemical reaction with it. Hence, the FB must be excluded from consideration as a direct inducer of cellular neoplastic potential and determination (Table 1).

What then could be the etiological key factor or event in FB tumorigenesis? If there is any obvious factor that exerts a noticeable direct influence on cells of the local environment that partakes in the FB reaction it is the dynamics of the FB reaction itself, which stimulates cellular mobilization, proliferation, and functional activity. How could it be possible that neoplastic potential and determination are created under these circumstances (Chart 2)? It may be through a spontaneous error within the regulation system of the cell, especially when it divides. The likelihood of such an event would increase during forced cell proliferation as it occurs in FB reaction (Chart 2A). On the other hand, the event may take place also under normal conditions when cells proliferate at a regular pace. This would mean that preneoplastic cells may be residing in the tissue prior to the introduction of the FB (Chart 2B). Both situations are consistent with available data and are presently subject to further experimentation.

Whenever such an error occurs in the cellular regulation system, loss of growth control with autonomous proliferation is apparently not an immediate outcome because there is always a long period of tumor latency. Therefore, we have to assume that the error remains unexpressed or that the cell is able to compensate for the defect for some time.

Why is it that specific cells, presumably of the microvasculature, acquire neoplastic potential and determination while other cell types, such as macrophages and fibroblasts, appear or proliferate under the same stimuli in FB reactions to a much greater extent? A possible explanation is that some cell types of the microvasculature may have a unique inherent predisposition. On the other hand, they represent undifferentiated proliferative mesenchymal stem cells with a long life-span individually, according to our observations. Although spontaneous errors may occur in cells of any type,

Table 1

<table>
<thead>
<tr>
<th>Stage</th>
<th>Role of FB</th>
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<tbody>
<tr>
<td>I</td>
<td>Initiation of FB reaction: mobilization, functional activation, proliferative stimulation of cells characteristic of FB reaction, among them preneoplastic parent cells presumably associated with the microvasculature.</td>
</tr>
<tr>
<td>II - III</td>
<td>Perpetuation of FB reaction causing conditions required for maturation of preneoplastic clonal cells. (Stimulation of fibrosis with formation of a collagen-rich tissue capsule; phagocytic inactivity of macrophages attached to nondegradable FB).</td>
</tr>
<tr>
<td>IV</td>
<td>Availability of FB surface for attachment of preneoplastic clonal cells as required for attaining neoplastic autonomy.</td>
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Chart 2. Possible time relationships between origination of preneoplastic parent cells and FB implantation. See text for explanations and definitions.
they would not become manifest if the error has a delayed expression and the cells belong to the category of differentiated dead-end cells with short life-spans.

Second Stage: Preneoplastic Maturation Phase Depending on Fibrosis of FB Reaction

Experimental Findings. The transition from the 1st to the 2nd stage of FB tumorigenesis is gradual and takes place during the 2nd month postimplantation. The main criterion of this stage is the formation of a grossly and microscopically distinct fibrous connective tissue capsule around the FB (Fig. 1b) (14).

Preneoplastic clonal cells (Chart 1, CC') are present in the capsule tissue and also in the loose connective tissue outside the well-demarcated capsule (9). However, attempts to demonstrate preneoplastic cells among the monolayer on the FB surface were consistently unsuccessful (8, 9).

Conclusions and Interpretations. While preneoplastic clonal cells go through the period of tumor latency, an intracellular maturation process towards acquisition of proliferative autonomy seems to take place in several steps, each step possibly dependent on certain specific environmental conditions.

During Stage II of FB tumorigenesis the FB itself still does not appear to interact directly with preneoplastic cells and must, therefore, be assumed to have no direct influence on the intracellular tumorigenic process. The role of the FB is obviously restricted to its continued presence in the tissue perpetuating the FB reaction, which converts into the more chronic fibrotic form (Fig. 1b; Table 1). This fibrotic element is consistently associated with the tumorigenic process as indicated by several observations and experiments. It has been shown that FB surface properties influence degree of fibrosis as well as tumor incidence and latency. For example, plastic film implants with sandpapered surfaces cause more cellularity, less fibrosis, fewer tumors, and longer latencies than do untreated smooth films (1). Also, if FB reaction remains for an extended time period in the acute fibrotic form (Stage I) due to prolonged aseptic inflammation or mechanical irritation, tumor appearance is markedly delayed (6). Furthermore, animal species differ in proneness to FB sarcomas and, again, this appears to be correlated with the degree of fibrosis in FB reaction (4). Whereas in rats and mice the FB reaction becomes fibrotic within 4 to 8 weeks, in man it takes up to 2 years, and in guinea pigs the initial fibrosis is resolved after a few months. It seems more than a coincidence that in man FB sarcomas are rare with latencies between 10 and 40 years (18) and that none have been observed in guinea pigs.

In face of the association between fibrosis and FB tumorigenicity, the process of fibrosis itself or factors that stimulate fibrosis must be considered to be of critical significance in FB tumorigenesis during Stage II and possibly during later stages as well. Such fibrogenic factors, which may be species specific, remain to be explored as to their tumor-promoting properties. An interesting lead has been suggested by recent experiments on mice in which Millipore filters of different pore sizes were used as implants (16). A conspicuous correlation was found to exist between phagocytic inactivity of FB-attached macrophages, fibrosis of the FB reaction, and FB tumor incidence.

It may be argued that fibrosis is an accompanying but basically unrelated feature of FB tumorigenesis. On the other hand, the obvious question arises whether fibrosis plays a direct and perhaps essential role in the tumorigenic maturation process. At the present time, only a very speculative answer can be given which, however, may serve as a working hypothesis in future investigations. We have to remember that the preneoplastic parent cells are presumably mesenchymal stem cells connected with the microvascularity. As such they are functionally involved in FB reaction through participation in vascular repair and capillary outgrowth. During the acute cellular stage of FB reaction, capillaries sprout freely into the loose inflammatory tissue for the purpose of extending the vascular network to where blood supply is needed. Then, during the subacute fibrotic stage, collagen is produced by fibroblasts and deposited in the capsule wall. The collagen-rich tissue contracts and compresses capillaries, which consequently obliterate. In this way, vascular segments or cells such as pericytes may become disconnected from their disintegrating structural base. They may find themselves without normal intercellular communication and tissue-specific control. Yet they may continue to proliferate and disseminate, which, as we have shown, is certainly true for the preneoplastic cells. At this point, the clonal nature and expansion of the preneoplastic cells can often be demonstrated by the kind of transfer experiment described earlier. Eventually, preneoplastic cells reach the FB surface and adhere to it. This conspicuous event marks the beginning of Stage III.

Third Stage: Preneoplastic Maturation Phase Depending on Chronic Quiescence of FB Reaction

Experimental Findings. The beginning of this stage is marked by the demonstration of transferable preneoplastic clonal cells (Chart 1, CC') in the cell monolayer firmly attached to the FB surface (9). The timing of this event is variable. The earliest demonstration, by transferring a plastic film implant, was accomplished on a single instance at 2.5 months postimplantation (8). The success rate does not approach 100% before the 7th month.

Homologous preneoplastic cells (belonging to the same clone) are usually also still present in the capsule tissue. However, while the preneoplastic cells will produce tumors when transferred with FB segments, tumors do not develop from transferred capsule segments alone unless a new piece of FB is inserted (5, 6, 9). When comparing latencies of homologous tumors from transferred FB segments and from capsule segments with new FB, no significant differences are apparent.

As described earlier, the FB reaction is at this time histologically and ultrastructurally stagnant and quiescent (Figs. 1c and 3) (7, 14), yet to some degree there is continuous DNA synthesis and proliferative activity in FB-attached cells (M. J. Thomassen, I. Brand, L. C. Buoen, and K. G. Brand, to be published). The preneo-
plastic cells must be among them because it was shown that, by transferring FB segments of minimum sizes at different times, preneoplastic cell clones continue to increase in size and expansion (9, 19).

**Conclusions and Interpretations.** The most conspicuous morphological characteristic of this stage is the quiescence of the FB reaction in general combined with the ultrastructural dormancy of the macrophage population. How this relates to preneoplastic maturation is difficult to assess at the present. The same factors that are responsible for stagnancy of tissue function and/or phagocytic inactivity of macrophages may in turn promote the maturation of preneoplastic cells; or phagocytic inactivity of macrophages by itself, in the continued presence of a FB, may create a functional stimulus for other cell types including collagen-producing fibroblasts and mesenchymal stem cells of the microvasculature possessing neoplastic determination.

The clarification of these questions needs further experimentation. Fundamental for the understanding of Stage III, however, is the recognition of the fact that, even though part of the clone has established firm contact with the FB surface, this is not yet a requirement for the maturation of preneoplastic cells to proceed (Chart 1; Table 1). Evidence was obtained through the observation that tumor latencies are virtually of equal duration whether homologous preneoplastic cells were transferred with a FB segment or with a capsule segment plus a new FB insert. Hence, it must be assumed that the homologous cells remaining in the capsule tissue continue their preneoplastic maturation at the same pace as does the FB-attached part of the clone.

**Fourth Stage: Preneoplastic Maturation Phase Depending on Direct Contact of Cells with the FB Surface**

**Experimental Findings.** Stage III ends and Stage IV begins when direct FB contact becomes the prerequisite for preneoplastic cells to mature beyond the point that can be reached by homologous cells in the capsule tissue (Chart 1, CC"m"). Firm attachment of preneoplastic cells to the FB surface (6, 9) is the essential criterion of Stage IV. In fact, FB contact is the prerequisite for finally attaining proliferative autonomy (Chart 1, CC; Table 1). As during Stage III, homologous preneoplastic cells may still be present in capsule tissue but will not give rise to tumors upon transfer unless a new FB is inserted (5). If that is done, however, preneoplastic cells will move out of the capsule tissue and soon settle on the new FB surface (K. G. Brand, L. C. Buoen, and I. Brand, to be published).

Stage IV, *i.e.*, the requirement of FB contact for completing preneoplastic maturation, is usually of short duration. This can be concluded from transfer experiments involving segments of advanced capsules plus new FB inserts. If such capsule segments contained preneoplastic cells arrested at the CC"m" point, it often took less than 2 months for palpable tumors to develop (5). But again, if segments of the same capsule were transferred without a new FB insert, the preneoplastic cells generally would not pass beyond the CC"m" point, not reach the state of proliferative autonomy, and not develop into tumors.

**Conclusions and Interpretations.** Stage IV then appears to be the only period of FB tumorigenesis during which physical contact between FB and preneoplastic cells becomes the essential feature. The nature of the interaction remains to be investigated. Presumably, the critical effect that leads to proliferative autonomy of the cell occurs primarily at the level of the cell membrane when it firmly adheres to the FB surface. However, the crucial events during Stage IV, representing the final step in the acquisition of neoplastic autonomy, must not distract from the fact that specific neoplastic determination is a fixed property of the cells long before they come into direct contact with the FB surface.

As reported in the literature (17) and infrequently observed in our laboratory, removal of the FB implant from the tissue capsule during the late preneoplastic period does not always abort development of tumors from the remaining empty capsule. At least 2 explanations for this phenomenon come to mind: (a) the cells may have completed preneoplastic maturation and were already in the process of detaching from the FB surface as early tumor cells (Chart 1, CC"a" or TC); or (b) the cells were still in Stage III. However, removal of the FB left a solid collagenous, possibly even calcifying or ossifying, scar that failed to resolve and therefore acted like FB material. The latter explanation may underline the occurrence of scar-related sarcomas in man, as reported in the literature (18).

**Fifth Stage: Cellular Autonomy and Neoplasia**

**Experimental Findings.** Stage V begins when preneoplastic cells have acquired autonomy (Chart 1, CC"a"). The proliferating cells detach from the FB surface and invade the capsule tissue. In time, a tumor develops.

**Conclusions and Interpretations.** The events at this stage are straightforward once growth control of the cells involved breaks down. Yet, it must be assumed that there is always some delay between reaching the stage of cellular autonomy (Chart 1, CC"a") and the beginning of structured tumor growth (Chart 1, TC). The delay may be dependent on intracellular factors or, like other phenomena described in the foregoing, on environmental conditions. A possibly related observation is regularly made in transplantation experiments with established FB-induced tumors using minimal numbers of isolated viable cells. We found that tumor passage was rarely successful when the cell number was below 5000 (L. C. Buoen, V. N. Michelich, and K. G. Brand, unpublished observation). Apparently, a critical mass of tumor cells is necessary to organize and coordinate the stroma of the recipient and the injected tumor cells in such a way that tumor formation can occur. The possible role of specific immunity in this situation is unlikely because of weak or nonexistent tumor-specific antigenicity of FB-induced tumors in general (10).

In this context the question may be asked whether preneoplastic maturation is really an intracellular process as complex and involved as interpreted in our preceding discussions. Could it be that what we call the period of "preneoplastic maturation" or "tumor latency" only re-
reflects gradual amassment of cells that are perfectly neoplastic a priori until they reach the critical number necessary for tumor formation? This does not seem likely to us since preneoplastic maturation appears to be stringently linked to a fixed sequence of varied essential conditions that are precisely met in the tumorigenic stages described. Such strict sequential dependencies hardly should be required for only allowing cells to increase in number.

REFERENCES


Fig. 1. a, reactive connective tissue adjacent to the FB at I month postimplantation. The tissue reaction is characterized by the presence of macrophages, neutrophils, fibroblasts, and many capillaries. Collagen production is minimal, H & E, x 280. b, portion of connective tissue capsule surrounding the FB 3 months postimplantation. The tissue reaction is characterized by decreased cellularity with a relative increase in the number of fibroblasts and increased collagen production. H & E, x 280. c, portion of dense connective tissue capsule surrounding the FB 6.5 months postimplantation. Note pronounced collagen formation and limitation of blood vessels to the outer aspects of the capsule. H & E, x 230.

Fig. 2. a, cell monolayer attached to FB surface on the 12th day following implantation. Note macrophage-type cells including multinucleated giant cells and patches of neutrophils (arrows). May-Grünewald-Giemsa, x 220. b, cell monolayer attached to FB surface 5 months postimplantation. Macrophage-type cells including multinucleated giant cells still predominate. May-Grünewald-Giemsa, x 220.

Fig. 3. Electron micrograph showing portion of 2 FB-attached macrophages (7 months postimplantation) with numerous villous projections associated with the cell surface. The cytoplasmic matrix of the FB-attached cells is electron dense and contains numerous tubular lysosome-like structures (Ly). Open arrows, plane of cell attachment to FB surface. The surface of the connective tissue capsule is covered by a continuous layer of greatly extended fibroblast-like cells (Fib). Lead citrate and uranyl acetate, x 16,800.
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