Langhans' Giant Cells and Tubercle Bacilli
In 91 Pulmonary Tuberculous Lesions
Resected After Prolonged Combined Chemotherapy

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Introduction
The Langhans' giant cell described in 1868 is a large cell with numerous nuclei arranged in a ring around the periphery of an eosinophilic cytoplasm. The cytoplasm is homogeneous or granular and may contain inclusions such as Mycobacterium tuberculosis. The foreign body type giant cell can be distinguished by the presence of nuclei throughout the substance of the cytoplasm rather than at the periphery. Both cell types are found in the granuloma of tuberculosis as well as the granulomata of sarcoidosis, berylliosis, leprosy, syphilis, actinomycosis, histoplasmosis, coccidiomycosis, leishmaniasis and lymphogranuloma venereum.

Langhans' giant cells are thought to result from the fusion or incomplete, amitotic division of epithelioid cells (histiocytes). In clinical tuberculosis the intact M. tuberculosis is thought to be the agent responsible for the formation of giant cells. Lipid extracts (phospholipids) of the tubercle bacillus may cause a giant cell reaction but only with relatively large doses. Numerous other studies have attempted to determine the relative importance of the tubercle bacillus and the host factors in the giant cell reaction. Several recent studies have indicated that tubercle bacilli in caseous pulmonary tuberculous lesions gradually lose their ability to multiply. This happens with or without the influence of chemotherapy. Careful bacteriologic and histologic studies of 130 consecutive pulmonary tuberculous lesions resected after prolonged combined chemotherapy showed a high correlation between bacterial viability and histologic evidences of "activity," including epithelioid cells, lymphocytes, recent caseation necrosis, giant cells and minimal fibrous reaction. The correlation was particularly high for the 94 lesions without an open cavity.

The present study covers but one facet of the problem. It is an attempt to correlate the relative number of giant cells in small localized tuberculous pulmonary nodules with the results of bacteriologic analysis.

Material and Methods
The material available for this study was obtained during a 28-month interval (January 1951 to April 1953) from patients with bacteriologically proved pulmonary tuberculosis and subjected to various forms of resec-

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tional surgery. Nearly all patients received streptomycin and para-
aminosalicylic acid as part of their treatment prior to surgery. Isoniazid
was used in only a few. Ninety-one single pulmonary tuberculous nodules
removed by "wedge" or "subsegmental" resection were selected for study.
In order that the histologic study be thorough, nodules were selected in
which the greatest diameter of the diseased tissue did not exceed 2.5 centi-
meters.* Cavity lesions were not included.

Each piece of resected tuberculous tissue was divided into two equal
portions. One was submitted for bacteriologic study for tubercle bacilli.
Bacteriologic study included careful scrutiny of a smear of the homoge-
nized lesion; the Ziehl-Nielsen technique was used in staining. The ho-
mogenized lesions (both undigested and digested with 3 per cent NaOH)
were also cultured on Lowenstein's medium; the cultures were observed
for a minimum of two months before being discarded. Finally, digested
and undigested emulsions of the resected lesion were inoculated intra-
peritoneally into separate guinea pigs. The animals were sacrificed after
two months and their organs examined grossly and by smear for acid-fast
bacilli.

The remaining portion of each lesion was fixed in formalin, embedded
in paraffin, sectioned and stained with hematoxylin and eosin. At least
two paraffin sections of each lesion were studied for giant cells.

The histologic specimens were carefully scrutinized with special atten-
tion paid to the relative number of Langhans' giant cells. The specimen
was assigned to Group I only if the paraffin sections of the diseased tissue
contained not more than one giant cell in the entire paraffin section. The
specimen was classified in Group II if microscopic sections revealed the
presence of a few to many giant cells.

Group II specimens were heterogenous insofar as the relative number
of Langhans' giant cells was concerned. Giant cells were present in small
or large numbers. Moreover, the relative giant cell population varied in
different portions of the same lesion. Group I lesions were characterized
by the uniform and extreme paucity of giant cells.

Results

Table I illustrates the distribution of the 91 lesions according to the
giant cell population. The majority (72) of the specimens contained from
a few to many giant cells in an average low-power microscopic field
(Group II). Twenty per cent were devoid of giant cells in the paraffin
sections (Group I). The average duration of chemotherapy prior to sur-
gery was the same in each group.

There was a significantly greater incidence of viable tubercle bacilli
in lesions containing giant cells than in the group of lesions devoid of
giant cells (Table I). Further analysis of the 72 lesions in Group II re-
vealed that the incidence of bacterial viability did not vary significantly
with the relative number of giant cells. Lesions containing viable bacilli

*The present study included nearly all the 94 nodular lesions subjected to a more
detailed histologic analysis in a previous paper.11
TABLE I
DISTRIBUTION OF LANGHANS' GIANT CELLS IN 91 RESECTED TUBERCULOUS NODULES AND THE BACTERIOLOGY IN EACH GROUP

<table>
<thead>
<tr>
<th>No. of Langhans Giant Cells</th>
<th>No. of Lesions Containing Viable Tubercle Bacilli</th>
<th>No. of Lesions Containing Acid-fast Bacilli by Smear</th>
<th>No. of Lesions Negative for Acid-fast Bacilli by Smear and Culture</th>
<th>Mean Duration Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. per cent</td>
<td>No. per cent</td>
<td>No. per cent</td>
<td></td>
</tr>
<tr>
<td>Group I (0-1 per section)</td>
<td>19</td>
<td>0*</td>
<td>9 47</td>
<td>10 52 169 days</td>
</tr>
<tr>
<td>Group II (few to many per low-power field)</td>
<td>72</td>
<td>22*</td>
<td>47 65</td>
<td>19 26 174 days</td>
</tr>
<tr>
<td>Total</td>
<td>91</td>
<td>22 24</td>
<td>56 61</td>
<td>29 32</td>
</tr>
</tbody>
</table>

*The difference in frequency of viable organisms in Group I and Group II is statistically significant \( P = \leq .01 \).

always had giant cells; the same was not true of the lesions from which acid-fast bacilli were demonstrated by the smear technique. As indicated in Table I, nine of 56 smear-positive lesions were devoid of giant cells. Since positive smears for acid-fast bacilli reflect large numbers of tubercle bacilli in the lesions, it would appear that the number of organisms, *per se*, is not the sole factor governing the relative number of giant cells. The giant cell population appears to be related to the presence of viable tubercle bacilli. The reason for this is unknown.

The average duration of chemotherapy was longer with lesions having non-viable bacilli (189 days) than in the lesions with viable bacilli (121 days).

Comment

An attempt has been made to evaluate the significance of Langhans' giant cells in human tuberculosis by a simultaneous histologic and bacteriologic study of localized pulmonary nodules obtained by resectional surgery. By limiting the study to small solid lesions, one is assured that the bacteriologic and histologic specimens were anatomically related.

Smears of the resected non-cavitary lesions were more often positive for tubercle bacilli than cultures or guinea pig inoculations. This discrepancy has been attributed to chemotherapy as well as to the bacteriostatic effect of necrotic tissue products. The present study is in agreement with the experience of others in regard to the frequent non-viability of tubercle bacilli under these conditions in spite of their persistence on smears. An attempt has been made to evaluate the significance of Langhans' giant cells in human tuberculosis by a simultaneous histologic and bacteriologic study of localized pulmonary nodules obtained by resectional surgery. By limiting the study to small solid lesions, one is assured that the bacteriologic and histologic specimens were anatomically related.

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nodular lesions showed a high degree of correlation between bacterial viability and the "activity" of the lesion as judged by the pathologist.\textsuperscript{11}

The concept that viable tubercle bacilli stimulate the proliferation of giant cells has been proposed previously.\textsuperscript{2, 7} The above data would support such a concept. Most giant cells, however, do not contain visible acid-fast bacilli.\textsuperscript{10, 12} Giant cells are not necessarily all active phagocytes.

The 19 tuberculous lesions which were devoid of giant cells did not yield acid-fast bacilli which would multiply even though nine of these lesions showed acid-fast bacilli by the smear technique. This information suggests that in localized, non-cavitary, tuberculous lesions the absence of giant cells in some way is related to the inability of the tubercle bacilli to multiply.

Recently Denst reviewed the histopathology of far-advanced tuberculous lung lesions in five patients following isoniazid therapy.\textsuperscript{13} He reported numerous atypical foreign body type giant cells, frequent liquefaction of cavity contents and intense infiltration of tuberculous nodules with neutrophilic leucocytes. The present study includes only a few patients receiving isoniazid and there was no open cavitary lesion. Foreign body type giant cells were not numerous in our material. Neutrophilic leucocytes were seldom striking in the tuberculous nodules. Both the material and the histologic findings were quite different from those of Denst.

**SUMMARY**

Ninety-one surgically resected, non-cavitary tuberculous nodules with the greatest diameter not exceeding 2.5 centimeters were selected for histologic and bacteriologic analyses. Nineteen were characterized by almost complete absence of giant cells (Group I). The remainder (Group II) contained from a few to many giant cells in each paraffin section.

Although 47 per cent were positive by smear, none of the tuberculous lesions in Group I yielded viable acid-fast bacilli by culture or guinea pig inoculation. However, 31 per cent of the lesions in Group II contained viable acid-fast bacilli. This difference is statistically significant.

Within Group II no significant correlation was noted between the relative numbers of giant cells and the frequency of bacillary viability.

It is suggested that the absence of giant cells within a localized tuberculous nodule is related to the inability of the acid-fast bacilli within that nodule to multiply. Previous studies have shown that other evidences of histologic "activity" are also related to the viability of the tubercle bacilli.

**RESUMEN**

Noventa y un nódulos quirúrgicamente extirpados, con tuberculosis no cavitaria con diámetro, el mayor, de 2.5 cms. se escogieron para estudio bacteriológico e histológico. Diecinueve se caracterizaron la casi completa ausencia de células gigantes (grupo 1), el resto (grupo 2) contenían de pocas a muchas células gigantes en cada corte en parafina.

Aunque 47 por ciento fueron positivos al frotis ninguna de las lesiones tuberculosas del grupo 1, dieron bacilos viables por cultivo o inoculación
al cuy. Sin embargo, 31 por ciento de las lesiones del grupo 2 contenían bacilos viables, ácido resistente.

Esta diferencia es estadísticamente significante.

Dentro del grupo II no se encontró correlación significante entre el número relativo de células gigantes y la frecuencia de la viabilidad del bacilo.

Se sugiere que la ausencia de células gigantes en una lesión tuberculosa nodular está en relación con la incapacidad del bacilo dentro de ese nódulo, para multiplicarse. Estudios previos han mostrado que otras evidencias de actividad "histológica" están también en relación con la viabilidad del bacilo de la tuberculosis.

RESUME

Les auteurs ont choisi 91 pièces après résection chirurgicale. Il s'agissait de nodules tuberculeux non excavés, dont le diamètre principal ne dépassait pas 2 cm., 5. Ces pièces furent soumises à un examen histologique et bactériologique. 90 étaient caractérisées par l'absence à peu près complète de cellules géantes (groupe I). Les autres (groupe II) contenaient des cellules géantes dans chaque bloc de paraffine en quantité variable. Dans certains cas, il y en avait peu, dans d'autres, elles étaient très nombreuses.

Bien que 47% des cas contenaient des bacilles de Koch sur lames, aucune des lésions tuberculeuses du groupe I ne permet de mettre en évidence des bacilles acido-résistants viables, par cultures ou inoculations au cobaye. Toutefois, 31% des lésions du groupe II renfermaient des bacilles acido-résistants viables. Cette différence est statistiquement valable.

Permi les pièces du groupe II, les auteurs ne constatèrent pas une relation évidente entre la quantité des cellules géantes d'une part, et la viabilité des bacilles d'autre part.

Les auteurs émettent l'hypothèse que l'absence de cellules géantes dans un nodule tuberculeux est en relation avec l'impossibilité de la multiplication des bacilles acido-résistants dans ce même nodule. Des études antérieures ont montré que d'autres signes manifestes de lésions histologiquement actives se retrouvent parallèlement à l'existence de bacilles tuberculeux viables.

REFERENCES