The Pattern and Behavior of Pulmonary Tuberculosis in Diabetic Patients*

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The frequent association of diabetes mellitus and pulmonary tuberculosis has long been observed. Moreover, the incidence of tuberculosis in diabetics is more than in the general population. Windle, in a study of 333 necropsies of diabetics, gave an incidence of pulmonary tuberculosis in 50 per cent. Himsworth reported an incidence of 6.5 per cent pulmonary tuberculosis in routine x-ray films. Root stated that in children and young people, tuberculosis occurs about 12 times as frequently among diabetics as in nondiabetics. Boucot and associates found a prevalence of pulmonary tuberculosis of 8.4 per cent among 3,106 diabetic patients in Philadelphia, which was twice as high as the prevalence in a group of apparently healthy industrial workers. The variability of these figures is in all probability due to the differences in material and age groups.

The exact reason for such a high incidence of tuberculosis in diabetics is not known and only few suggestions have been made. Dubos quotes experimental evidence that ketosis is the most important factor in starvation which causes activation of the tuberculous foci; it seems reasonable to infer that this may be the case in diabetes. Banyai attributes this susceptibility to overproduction of A.C.T.H. with resultant lowered bacteriostatic capacity and deficiency in tissue repair, as well as to hepatic dysfunction with vitamin A deficiency which probably account for the high incidence of the exudative forms of tuberculosis in these patients. Poulsen considers overproduction of glycerol in diabetics to be a good source of energy for tubercle bacilli. Root stated that the cells of the reticuloendothelial system of patients dying in diabetic coma are completely filled with lipids which interfere with the immunobiologic reaction against infection.

This study is confined to the pattern of the tuberculous lesion (type, extent and location) encountered in diabetic patients as well as its behavior on treatment.

Observations

The total number of diabetics reviewed is 371 with bronchogenic tuberculosis, in all of whom a bacteriologic diagnosis was made. Only cases observed for a minimum of two years from the time of diagnosis of tuberculosis were included. The cases were treated from 1954 until 1960. There were 290 men and 81 women. The age range varied from 22 to 75, while only 19 cases were below the age of 45 years.

Characteristics of Diabetes

Diabetes was known to exist before tuberculosis in 280 cases (75 per cent) while both tuberculosis and diabetes were diagnosed simultaneously in 91 cases (25 per cent). In no case did diabetes “develop” after tuberculosis.

Referring to the state of control of diabetes before tuberculosis was diagnosed, it was poorly controlled in 232 cases out of 280 (83 per cent). This supports the old dictum that tuberculosis is the penalty of poorly controlled diabetes; however, this does not nullify that tuberculosis can occur even if diabetes is previously well controlled.

The duration of diabetes before pulmonary tuberculosis was diagnosed (280 cases), varied from four months to 16 years.

The degree of diabetes was mild in 38, moderate in 148 and severe in 185 cases. On an arbitrary basis, cases were considered mild if less than 30 units of insulin per

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day were needed, moderate if insulin requirement was between 30 and 50 units, and severe if more than this. Ketosis with or without coma was reported in 65 cases.

No correlation could be made between the length of the previously existing diabetes or its degree and the pattern or behavior of the tuberculous lesion. Ketosis was the only variable that could be consistently related to the behavior of tuberculosis on treatment.

Soluble insulin was initially used for control of diabetes; the principle adopted was to avoid ketosis and to keep sugar in urine at a minimal level. No attempt was made to keep urine completely free from sugar, since this achievement usually exposed patients to hypoglycemic reactions. A fasting blood sugar of 120-180 mg per cent with slight trace of glycosuria was considered satisfactory. Subsequent to the initial control, other insulins or oral hypoglycemic drugs were used. Sulphonylurea derivatives and phenformin were used for 56 cases of mild diabetes more than 40 years of age which were nontoxic and not febrile and with no history of ketosis. Phenformin was used for cases of "brittle diabetes" to prevent the wide excursions of blood sugar and for sulphonylurea failures (seven cases).

The results of oral hypoglycemic drugs are shown in Table 1.

**Table 1—Results of Oral Hypoglycemic Agents in 56 Cases (63 Treatments)**

<table>
<thead>
<tr>
<th>Oral Hypoglycemic Agent</th>
<th>Total Number</th>
<th>Maintained Response</th>
<th>Failure (Primary or Secondary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphonylurea</td>
<td>27</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Phenformin alone</td>
<td>15</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Phenformin with insulin</td>
<td>14</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Sulphonylurea failures</td>
<td>7</td>
<td>7</td>
<td>—</td>
</tr>
</tbody>
</table>

Neither the response of the tuberculous lesion nor its state of activity were different in cases receiving oral hypoglycemic agents from those treated with insulins.

**Characteristics of Tuberculosis**

Tuberculosis was suspected because of one or more of the following symptoms: cough and sputum (112 cases), hemoptysis (196 cases), fever (74 cases), general weakness (52 cases), difficulty in controlling diabetes (32 cases) and at a check-up (16 cases). It is notable that hemoptysis occurred in 50 per cent of cases as a presenting symptom which is more than its general incidence in non-diabetic tuberculosis.

Sosman and Steidl spoke of hilar and lower lobe tuberculosis as "diabetic tuberculosis." In this report, the distribution of tuberculous lesions was in the upper zones in 164 cases; lower zones in 54 cases; hilar in 38 cases and mixed in 115 cases. As to the type of lesions, these were mainly exudative, but also fibrotic and productive lesions were also encountered. Further details related to the presence of cavities and localization are given in Table 2.

**Table 2—Type and Extent of Lesions at the Time of Diagnosis of Tuberculosis**

<table>
<thead>
<tr>
<th>Extent of Lesion</th>
<th>Type of Lesion</th>
<th>Minimal</th>
<th>Moderately Advanced</th>
<th>Far Advanced</th>
<th>Total Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral non-cavitary</td>
<td>65</td>
<td>27</td>
<td>—</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Unilateral cavitary</td>
<td>11</td>
<td>61</td>
<td>70</td>
<td>142</td>
<td></td>
</tr>
<tr>
<td>Bilateral non-cavitary</td>
<td>22</td>
<td>11</td>
<td>—</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Bilateral cavitary</td>
<td>—</td>
<td>25</td>
<td>79</td>
<td>104</td>
<td></td>
</tr>
</tbody>
</table>

*Lesions classified as cavitary or non-cavitary as judged from plain x-ray films.

**Initial Chemotherapy**

At least two combinations of the following drugs were used simultaneously: streptomycin, para-aminosalicylic acid or isoniazid. Whenever streptomycin was used other than daily, both of the two other drugs were also given. The length of chemotherapy varied from six months to two years. No attempt was made to study possible superiority of certain combinations...
of chemotherapy over others. Regular chemotherapy was given to 280 patients while 91 patients received chemotherapy irregularly. The behavior of tuberculous lesions varied according to the regularity of antituberculosis drugs, the degree of control of diabetes, as well as the type and extent of tuberculosis (Table 3). Tuberculosis in cases having regular chemotherapy showed the highest regression rate, i.e., 83 per cent when diabetes was also controlled and 64 per cent with uncontrolled diabetes. In contrast, in cases of interrupted chemotherapy, tuberculosis showed lower rates of regression, i.e., 23 per cent and 10 per cent respectively. It seems reasonable to conclude that the main factor is the regularity of chemotherapy; the control of diabetes comes next in importance.

Cases showing progression of tuberculous lesions in spite of regular chemotherapy and satisfactory control of diabetes may be those with resistant organisms, and similarly cases which showed relapse after initial regression.

Ketosis seems to be an important factor in influencing behavior of the tuberculous lesions; among 80 with progressive disease in all groups, 52 were of those with ketosis and/or coma.

It is of interest that 33 patients of those on interrupted chemotherapy (91 cases) showed regression on the institution of sustained chemotherapy.

While no correlation could be seen between the duration and severity of diabetes and the behavior of tuberculosis on treatment, a substantial relationship could be demonstrated between the type and extent of disease and its response to chemotherapy. As might be expected, non-cavitary cases (whether unilateral or bilateral) did better on the whole than cavitary cases; notably these are minimal or moderately advanced cases. Considering all variables, the best course was met with, in exudative minimal lesions, regular chemotherapy and satisfactory control of diabetes. It might also be inferred that these are the early lesions. This shows the need for frequent check-ups in diabetics to detect their chest lesions before cavitation and progression of disease occur.

**Re-treatment**

Of 143 patients who did not show a steady regression, 115 were re-treated. Either a combination of the three standard antituberculosis drugs (72 cases), or drugs of the second line (ethionamide, cycloserine and kanamycin) (43 cases) were used. Except for the presence of resistance and/or ketosis, a high rate of regression was noticed (73 out of 115) in re-treated cases (63 per cent)—Table 4.

**Surgery**

Thosteson and McKean operated in pre-chemotherapy days on 11 patients with diabetes and tuberculosis with a fatality

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**Table 3—Behavior of the Tuberculous Lesions on Initial Treatment with Chemotherapy**

<table>
<thead>
<tr>
<th>Treatment Status*</th>
<th>Regression</th>
<th>Progression</th>
<th>Stationary</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Per cent</td>
<td>Number</td>
<td>Per cent</td>
</tr>
<tr>
<td>REGULAR CHEMOTHERAPY:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled diabetes</td>
<td>151</td>
<td>83</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Uncontrolled diabetes</td>
<td>64</td>
<td>64</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>INTERRUPTED CHEMOTHERAPY:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled diabetes</td>
<td>7</td>
<td>23</td>
<td>15</td>
<td>50</td>
</tr>
<tr>
<td>Uncontrolled diabetes</td>
<td>6</td>
<td>10</td>
<td>43</td>
<td>71</td>
</tr>
</tbody>
</table>

*Cases with interruption of chemotherapy of less than one month and not more than twice were included in the regular group.
rate of 27 per cent (thoracoplasty). Edge\(^a\) reported the results of 11 cases (seven thoracoplasties, two segmental resections, one pneumonec-tomy and one decortication); all survived operative and postoperative stages. Seven of these 11 cases had antimicrobial treatment.

In this series, thoracoplasty was done for 17 cases: 12 after initial treatment and five after re-treatment. Resection in the form of lobectomy was done for six after initial treatment and six after re-treatment. There was no difference in the results of cases operated upon after initial chemotherapy as compared with those who were re-treated. All the 29 for whom surgery was done were well and arrested at the end of the observation period.

### Results of Treatments at the End of Two Years

There were 257 with arrested lesions (69 per cent), 91 with active lesions and 23 deaths at the end of the observation period. It is striking that the highest rate of arrested lesions was in cases showing regression on initial chemotherapy (196 cases).

Deaths were mainly in the group with progressive changes on initial therapy (18 out of 23) while among cases with regression, only one case died. The fatality rate at the end of the observation period was 6.5 per cent; the immediate causes of death were fatal hemoptysis (seven cases), tuberculous bronchopneumonia (seven cases), coma (four cases) and nontuberculous causes (five cases).

### Summary

A review of 371 cases of bronchogenic tuberculosis in diabetics was made; all cases were treated by chemotherapy and observed for two years. Diabetes was either known to exist before tuberculosis or both diseases were discovered simultaneously. The pattern of tuberculosis lesions was not found to be characteristic of diabetes. No correlation was found between the duration of diabetes before tuberculosis or its severity and the pattern or behavior of the tuberculous lesion on treatment. Ketosis was an important factor affecting the response to chemotherapy. Oral hypoglycemic agents were found valuable in 56 cases whose course and end-result did not differ from comparable cases treated with insulin alone.

Strict adherence to regularity of chemotherapy is the most important factor bearing on the final outcome of these cases. Surgical intervention is safe in tuberculous diabetics if properly indicated and if done at the optimum time. The results at the end of two years were favorable (69 per cent arrested lesions) and the fatality rate was 6.5 per cent.

### Resumen

Se revisaron 371 casos de tuberculosis en diabéticos tratados durante dos años. La diabetes en algunos casos fue conocida previamente o bien se descubrió al mismo tiempo que la tuberculosis. El aspecto de la tuberculosis no tuvo características propias de la diabetes. No hubo correlación entre la duración de la diabetes antes de la tuberculosis o su gravedad y el cuadro evolutivo de la lesión bajo tratamiento. La ketosis fue un factor de importancia que afecta la
resposta a la quimioterapia. Se encontraron de valor los agentes hipoglucemiantes en 56 casos cuya evolución y resultado final no disfryeron de los casos comparables tratados con insulina sola. La regularidad de la quimioterapia es el factor más importante para definir la suerte final de estos casos. La intervención quirúrgica es segura en los diabéticos tuberculosis si está indicada y si se hace en el tiempo óptimo. Los resultados, al final de dos años, fueron favorables (90 por ciento con lesiones detenidas) y la mortalidad fue de 6.5 por ciento.

RESUMÉ

L'auteur a revu les observations de 371 cas de tuberculose bronchique chez des diabétiques; tous les cas furent traités par chimiothérapie et suivis pendant deux ans. Tantôt le diabète était connu antérieurement à la tuberculose, tantôt les deux affections furent découvertes simultanément. L'aspect des lésions tuberculeuses chez les diabétiques n'avait pas de caractère propre. Il n'y avait aucun rapport entre la durée du diabète avant la tuberculose et sa gravité, et le comportement de la lésion, tuberculose sous l'influence du traitement. La cétose fut un facteur important affectant la réponse à la chimiothérapie. Des produits hypoglycémiantes par voie buccale donnèrent des résultats valables chez 56 cas dont l'évolution et la condition finale ne différaient pas de cas comparables traités par l'insuline seule.

La régularité de la chimiothérapie est le facteur le plus important qui influe sur l'issue finale de ces cas. L'intervention chirurgicale est sans danger chez les diabétiques tuberculeux si elle est judicieusement indiquée et si elle est faite en temps opportun. Les résultats à la fin de deux années de surveillance furent favorables (60% porteurs de lésions jugulées) et le taux de mortalité fut de 6.5%.

ZUSAMMENFASSUNG


Eine regelmässige Chemotherapie ist der allerwichtigste Faktor, der über das schicksal die Schicksal dieser Fälle entscheidet. Chirurgisches Vorgehen ist ohne Gefahr bei Diabetikern mit Tuberkulose, wenn die Indikation genau gestellt wird und der Eingriff zum optimalen Zeitpunkt erfolgt. Die Ergebnisse nach Ablauf von 2 Jahren waren günstig (60% mit dem Stillstand gekommen Befunden), und die Sterblichkeit betrug 6.5%.

REFERENCES


DISSECTING ANEURYSM IN PREGNANCY

A 33-year-old woman incurred dissecting aneurysm of the aorta concurrently with the onset of labor, which was complicated shortly thereafter by occlusion of the left iliac artery and acute aortic insufficiency. After cesarean section, distal decompression of the false lumen was performed, and circulation was restored to the leg. Repair of the proximal intimal tear and of the defect of the aortic valve was delayed for three weeks to permit resolution of the changes in the aortic wall that may follow dissection and make suturing difficult.