Further Developments in Human and Bovine Antituberculosis Chemoprophylaxis with Isoniazid in Italy*

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ANIMAL OBSERVATIONS

Prior to dealing with human chemoprophylaxis, pertinent items will be presented to clarify the relationship between chemoprophylaxis and immunologic potentials of the body. Two series of experiments were conducted by Rosati and Badioli to determine whether: (1) cattle exposed to tuberculosis and treated with INH were protected against the disease; (2) if they developed immunity against subsequent parenteral infection with tubercle bacilli. Four calves vaccinated with BCG, four calves which had acquired tuberculosis through exposure and were subsequently treated with INH (10 mg./kg. daily in intermittent cycles devised by the author), and three controls were infected with virulent tubercle bacilli given intracutaneously. Isoniazid treatment was discontinued seven days before the exogenous reinfection. Clinically, the controls showed symptoms of evolving tuberculosis, while the other two groups, after a brief febrile period, manifested no signs of illness. Correspondingly, the site of inoculation with tubercle bacilli showed pronounced swelling with regional lymphadenitis in the controls. Only moderate corresponding changes were seen in the BCG and INH groups. In the latter two, necropsy two months after the start of this project revealed only a small tuberculous lesion at the site of inoculation and in the adjacent lymph nodes, while in the controls, there was a caseous primary complex and rapid generalization. This illustrates that the protective value of intermittent INH treatment corresponds to that of BCG vaccination. When chemoprophylaxis had been instituted before conversion to positive tuberculin skin reaction, pathologic changes were less than in the controls, but more than in the BCG and INH groups treated after tuberculin conversion.

In the second study, five months elapsed between discontinuance of chemoprophylaxis and exposure of the animals to exogenous infections. Six calves contracted tuberculosis through exposure to cattle with active disease, and after 40 days of contact, they were given INH, 10 mg./kg. daily as follows: two months on, 50 days off in non-infectious surroundings, two months on, 30 days’ interruption, one month on. At the end of this treatment, tuberculin skin tests were negative. After a five and one-half month interval, the calves were given 75 mg. tubercle bacilli parenterally. The same dose of reinfection was given to four calves that had received BCG five months previously. Four calves were used as controls after having acquired tuberculosis through exposure to diseased cattle, and four were given 75 mg. of tubercle bacilli. The last two groups received no INH. Clinical and pathologic manifestations were most pronounced in the last group of animals. The four BCG-treated calves showed no clinical evidence of disease, had moderate weight gain, and a moderate inoculation granuloma. Six calves given chemoprophylaxis had an entirely negative clinical course, moderate gain in weight, and a small inoculation granuloma. All animals were sacrificed 60 days after virulent reinfection. Findings on necropsy were comparable to those of the first experiment. The controls showed generalized tuberculosis with impressive local caseous primary complex.

Among the four controls of the first natural infection which were reinfe...
ent lymphohematogenous diffusion to the mediastinal ganglia could be observed in two animals, and flare-up of the first infection foci in the other two.

In the four BCG-vaccinated calves and in the six submitted to chemoprophylaxis, tuberculosis was limited to the inoculation granuloma and to the prescapular satellite lymph nodes which were moderate, particularly in the INH-treated animals.

Histologic examination did not reveal any specific lesion. Guinea pig inoculation with emulsions of pulmonary and mesenteric lymph nodes with no macroscopic lesion were negative in two of the six calves submitted to chemoprophylaxis and partly positive in some lymph nodes of the last four. The guinea pig inoculation showed tubercle bacilli in almost all the lymph nodes of the BCG-vaccinated calves. On the whole, we may say that in the last two groups of calves, tuberculosis caused by massive exogenous reinfection was stopped at its entry, and diffusion to the internal organs was avoided. Even without available histologic and bacteriologic findings of the second experiment, I believe we may conclude that these experiments on calves are of great importance in the field of human and bovine antituberculosis prophylaxis and demonstrate that secondary chemoprophylaxis with isoniazid can potentiate the natural immunity brought by a first infection and can act even after the discontinuance of administration of the drug.

**Human Observations**

Chemoprophylaxis of tuberculosis is being tested in numerous countries. In Italy, it was started under my direction and with the direct collaboration of Praloran, Oricchio, Lucchesi and Spina, in the first months of 1956 on guinea pigs, calves and
Provincial antituberculosis centers practicing chemoprophylaxis regularly
Provincial antituberculosis centers practicing chemoprophylaxis without recording data
Provincial antituberculosis centers practicing no chemoprophylaxis

human beings. Subjects with manifest primary tuberculosis were excluded and the study limited mainly to allergic subjects with latent tuberculosis and, to a limited extent, to tuberculin-negative cases exposed to massive contagion, but without active clinical or radiologic manifestations. The report presented by us at the Italian Congress of Phtisiology in September, 1956 was the first in the scientific world and has been followed by numerous other reports of our antituberculosis preventive method. In July, 1957, we proposed, for the first time, chemoprophylaxis by means of isoniazid in miners with incipient silicosis so as to decrease the high incidence of tuberculosis among them. The cases under observation have been selected from among 120,000 subjects submitted to clinical, radiologic and allergometric examinations, care being taken that the children chosen were mainly tuberculin-positive and from families of tuberculous patients, or were living with tuberculous individuals or with ex-patients, or who belonged to families whose members work in sanatoria, or were admitted to preventoria, colleges, homes and open-air schools.

The Italian National Social Providence Institute has financed, since 1957, five chemoprophylaxis centers in various parts of Italy (Fig. 1). This service is now also extended to practically all the Provincial Antituberculosis Centers (Fig. 2).

**SCHEME OF INH-ADMINISTRATION**

**according to Prof. A.OMODEI ZORINI method**

**SCHEME 1**

<table>
<thead>
<tr>
<th>Period of INH Administration</th>
<th>INH DOSE: 10 mg/Kg/DAILY- Mx mg 400</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUBJECTS LIVING IN LIGHT OR NON INFECTIOUS ENVIRONMENT</td>
<td></td>
</tr>
</tbody>
</table>

**SCHEME 2**

<table>
<thead>
<tr>
<th>Period of INH Administration</th>
<th>INH DOSE: 10 mg/Kg/DAILY- Mx mg 400</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUBJECTS LIVING IN HIGHLY INFECTIOUS ENVIRONMENT</td>
<td></td>
</tr>
</tbody>
</table>
New regulations of the Ministry of Public Health and of the National Social Providence Institute strongly recommend chemoprophylaxis, especially for those leaving sanatoria, in an effort to avoid relapses or at least to diminish the risk.

In tuberculin-positive subjects and in the absence of absolute risk of tuberculous contagion, it was deemed opportune to dispense INH with a daily dose of 10 mg./kg., taken in two doses, six days a week, in periods of three months each, alternating with intervals of therapeutic rest. Treatment should last two years in all. Yet, in the case of a serious contagion risk, we also deem it proper to extend the daily protective treatment to periods of six to nine to twelve months or even more, depending upon the circumstances (Fig. 3). Justification of the method of intermittent cycles is based upon the following considerations: (1) in spite of good tolerance to isoniazid, we try to avoid the eventual appearance of toxic phenomena in long periods of daily medication; (2) we have taken into consideration the psychologic difficulty of obtaining from the family the strictest adherence to treatment during periods exceeding three consecutive months; (3) we have tried to leave undisturbed the development of a relative immunity due to primary infection, particularly in tuberculin-negative subjects, or in those with recent change in the tuberculin reaction.

On the basis of the experimental investigations, we must point out that during intervals without INH, mycobacteria which have escaped the effect of the previous treatment cycle, or those coming from the

\[ \text{TREATED} \hspace{0.5cm} \text{CONTROLS} \]
\[ n=10,760 \hspace{1cm} n=5,642 \]

\[ \begin{array}{c}
\text{AGE} \\
0-5 \hspace{1cm} 6-10 \hspace{1cm} 11-15
\end{array} \]
\[ \begin{array}{c}
\text{TREATED} \hspace{1cm} \text{CONTROLS}
\end{array} \]
\[ \begin{array}{c}
\% \\
100 \hspace{1cm} 90 \hspace{1cm} 80 \hspace{1cm} 70 \hspace{1cm} 60 \hspace{1cm} 50 \hspace{1cm} 40 \hspace{1cm} 30 \hspace{1cm} 20 \hspace{1cm} 10 \hspace{1cm} 0
\end{array} \]
outside, may stimulate the organism in its own defenses. As soon as this new wave of germs would try to damage the host organism, the alternate therapeutic cycle checks their action. Vitamin B complex is given as an adjunct to isoniazid in order to avoid avitaminosis and neurotoxicity.

Up to June 30, 1961, 16,402 subjects of both sexes were studied (with slightly more men than women), of which 65.5 per cent were treated and 34.4 per cent were controls (Figs. 4 and 5). Some of the controls were given placebos, others nothing. In both groups, treated patients and controls, there was a prevalence of adolescents (nearly half the total); second most numerous were children of elementary school age, and last, children under five years of age. In the group treated with isoniazid, 51.6 per cent of the subjects lived in tuberculous family surroundings or with strong contagion. In the control group, this was the situation in 40.3 per cent (Fig. 6). We deliberately put ourselves in an unfavorable initial position relative to good results with chemoprophylaxis.

Initial tuberculin reaction (Fig. 7) was positive in the great majority of cases (77 per cent). Thus, we applied essentially secondary chemoprophylaxis according to McDermott. Yet, in many doubtful cases of suspected pre-allergic phase and in tuberculin-negative subjects living in contact with tuberculous people, we applied isoniazid treatment (primary chemoprophylaxis) in 2,507 subjects. Former tuberculous or pleuritic subjects were submitted to chemoprophylaxis in order to avoid relapses. Also included were psychiatric patients and silicotic miners (Fig. 8).

At the chemoprophylaxis centers in Latium and the Aosta Valley, 10,272 people were observed: 6,567 treated and 3,705 controls (Fig. 9), with the same distribution of age (Fig. 10) and family contact (Fig. 11). As to tuberculin sensitivity, 79.4
FIGURE 8: PARTICULAR INDICATIONS FOR CHEMOPROPHYLAXIS

<table>
<thead>
<tr>
<th>Subjects Under Observation</th>
<th>Centres of Lazio</th>
<th>Centres of Sardegna</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formerly tuberculous subjects</td>
<td>300</td>
<td>—</td>
<td>300</td>
</tr>
<tr>
<td>Formerly tuberculous pregnant women</td>
<td>250</td>
<td>6</td>
<td>256</td>
</tr>
<tr>
<td>Subjects formerly treated with pulmonary resections</td>
<td>11</td>
<td>56</td>
<td>90</td>
</tr>
<tr>
<td>Post-pleuritic subjects</td>
<td>200</td>
<td>30</td>
<td>230</td>
</tr>
<tr>
<td>Silicotic subjects</td>
<td>—</td>
<td>788</td>
<td>1,158</td>
</tr>
<tr>
<td>Psychopathic subjects</td>
<td>400</td>
<td>—</td>
<td>400</td>
</tr>
<tr>
<td>Total</td>
<td>1,161</td>
<td>880</td>
<td>2,434</td>
</tr>
</tbody>
</table>

INVESTIGATION IN THE CENTRES OF LAZIO AND VAL D’AOSTA

SUBJECTS UNDER OBSERVATION n=10,272

TREATED n=6,567

CONTROLS n=3,705

per cent were tuberculin-positive and 20.6 per cent tuberculin-negative; of both categories, about two-thirds were treated with isoniazid, and one-third with a placebo (Fig. 12). In reference to the intensity of the tuberculin reaction (Fig. 13), the majority were under 10 mm. in diameter and the minority had strong or violent reaction. Prolonged isoniazid treatment did not appreciably modify the pre-existing allergic state which remained unchanged in more than half the cases: in treated subjects, 57 per cent; in controls, 62 per cent (Fig. 14). Conversion of the tuberculin reaction to negative occurred in 12 per cent of the treated subjects, and in 9 per cent of the controls.

SUBJECTS GROUPED ACCORDING TO AGE

TREATED

CONTROLS

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We may say that when the allergic state is not of recent origin, isoniazid—although it controls the primary complex—does not result in sterilization of the organism. More interesting is the observation of the group of subjects who were tuberculin-negative initially and who became tuberculin-positive during the observation period: 13 per cent of the treated subjects, and 25 per cent of the controls. In this connection, we must bear in mind that children submitted to treatment and living in contagious surroundings were more numerous than the controls. Isoniazid helped lessen infection risk even in these cases. Actually, the frequency of clinically evolutive tuberculous forms was quite different in the two groups of children, to the obvious advantage of those treated with isoniazid.

In 6,567 subjects submitted to chemoprophylaxis during one to four years of observation, 12 cases of tuberculous disease (ganglio-pulmonary as well as extrapulmonary) developed a frequency of 0.18 per cent, while in 3,705 controls, 45 cases were observed, a frequency of 1.21 per cent (Fig. 15). We may say, therefore, that in
CHANGES IN TUBERCULIN REACTIONS

N= conversion to negative; A= increased; D=decreased; I=no change in reaction; P=conversion to positive

FIGURE 14

Of 3,132 subjects treated in tuberculous surroundings, ten became ill (0.31 per cent) against 29 controls from a group of 1,349 (2.14 per cent). In healthy family surroundings, two cases of tuberculosis were found in 3,435 treated cases (0.058 per cent), while in the controls, 16 of 2,350 were observed (0.68 per cent), (Fig. 16).

Of 5,198 tuberculin-positive subjects treated with isoniazid, six became ill (0.11 per cent), against 27 controls from 2,958 (0.91 per cent), (Fig. 17). In the tuberculin-negative subjects, an appreciable difference could also be noted: six of 1,369 treated subjects became ill (0.44 per cent), against 18 of 747 controls (2.4 per cent), which indicates that primary chemoprophylaxis can also be valuable in particular cases.

Figure 18 illustrates the clinical forms which appeared in our treated subjects, as well as in the controls. It appears that isoniazid treatment had more inhibitory influence on the primary adenopathies and on the pulmonary and extrapulmonary hematogenous forms of tuberculosis, such as miliary tuberculosis, pleurisy, osteoarticular tuberculosis, while it was less effective in preventing post-primary pulmonary infiltrative forms.

<table>
<thead>
<tr>
<th>Figure 15: Incidence of Clinically Active Tuberculosis Forms No. 10,272</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>6,567</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Figure 16: Incidence of Clinically Active Tuberculosis Forms with Regard to Environment No. 10,272</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environment</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>Infectious</td>
</tr>
<tr>
<td>Non-infectious</td>
</tr>
</tbody>
</table>

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Chemoprophylaxis in Silicosis

In July, 1957, I advocated chemoprophylaxis in miners affected with silicosis or siderosis. Monaco, one of my associates, favors the following range of application: (1) silicotic subjects with strongly positive tuberculin reaction living in non-infectious surroundings and without clinic-radiologic signs of active tuberculosis; (2) silicotic subjects living in contagious surroundings where family members or other people are affected with active tuberculosis; (3) silicotic subjects with family or personal history of previous tuberculous manifestations, even if not detectable by clinic-radiologic and laboratory examinations; (4) silicotic subjects with typical fibrocalcific pulmonary radiologic findings; and (5) silicotic subjects in the more advanced stages of pneumoconiosis (third stage and pseudotumor forms), in whom it is virtually impossible to discriminate radiologically how much of the lesion is due to pneumoconiosis and how much to tuberculosis.

The dosage was 500-700 mg. INH daily according to the weight of the subjects, with three-month cycles alternating without the drug, for two years. Cooperation was excellent and only 0.3 per cent of the subjects discontinued treatment. Tolerance of the drug was generally good and only in 2 per cent of the cases could transitory neuritis be observed. Of 788 cases treated during the four-year period, only nine cases of concomitant pulmonary tuberculosis occurred (1.14 per cent), while during the same period, of 370 controls selected at random, 26 became ill (7 per cent). This plan has been favorably received in France, Australia and Russia.

Indications for chemoprophylaxis by means of isoniazid are: (1) general preventive chemotherapy may be advisable in primitive areas and in countries with a
high rate of tuberculosis which lack anti-
tuberculosis organization; and also, when
an emergency situation has to be faced in a
given area before it is possible to secure
necessary means of treatment, methodic ex-
aminations and vaccination; (2) in similar,
but less serious situations, when it is possible
to carry out examination of the sputum,
skin testing and photofluorographic exam-
inations, selection of the cases may be pos-
able: evolutive tuberculous forms to be
treated with standard antibiotics, latent
forms with isoniazid alone, and tuberculin-
negative cases with vaccination (WHO
pilot projects in Africa); (3) in countries
where the incidence of tuberculosis is com-
paratively low and there are good dispens-
sary and sanatorium organizations, chemop-
rophylaxis has selective indications. In
such countries we recommend chemoprophylaxis as follows:
(a) for tuberculin-negative children and
adolescents exclusively when living with
tuberculous people and probably in pre-
allergic phase, prior to removal from sur-
roundings and to antituberculosis vaccina-
tion, if they remain anergic. On the other
hand, in the event allergic change takes
place, treatment with isoniazid and other
antibiotics should be pursued for at least
six months.
(b) in all tuberculin-positive children
under five years of age, even when living in non-infectious surroundings, and more
particularly, if tuberculin conversion is of
recent origin; in children over five years of
age and in adolescents belonging to fam-
ilies with a tuberculous background, espe-
cially if they are living with tuberculous
individuals.
(c) in tuberculin-positive subjects under
15 years of age living in any surroundings
whatsoever, during anergyizing grave ill-
nesses, and for three months after illness.
(d) in adults with recent tuberculin con-
version with tuberculin change as the only
manifestation, especially if they are living in
contact with tuberculous people.
(e) in tuberculin-negative, as well as
 tuberculin-positive adults who may be ex-
posed to tuberculous infection due to lab-
oratory accidents.
(f) among allergic adults affected with
chronic diseases requiring prolonged treat-
ment with corticosteroids.
(g) among silicotic and siderotic miners.
(h) in formerly tuberculous subjects who
happen to be in the following circum-
stances: (1) living in tubercle bacillus-
infect ed family or working at certain insti-
tutions (clinics, hospitals and sanatoria for
tuberculous, jails, mental hospitals, etc.);
(2) diabetics (during at least three years
after recovery); (3) during pregnancy and
puerperium (idem); (4) in subjects for-
merly suffering from pleurisy and peri-
tonitis (idem); (5) in formerly tubercu-
losus subjects already treated exclusively
with artificial relaxation therapy or surgical
measures without adequate chemotherapy.

SUMMARY
1. Calves submitted to chemoprophylaxis after primary infection resulting from
exposure to tuberculous cows acquired an
immunity which protected them against a
massive parenteral reinfec tion with bovine
tubercle bacilli. This immunity corresponds
to that obtained by BCG vaccination and
is present even if the reinfec tion occurs six
months after discontinuance of chemoprophylaxis.
2. Large-scale trials with chemoprophylaxis on human beings have been carried
out in Italy since April, 1956. Chemoprophylaxis has been used in selected groups
exposed to tuberculosis in households and
schools. These groups include all tubercu-
lin-positive children under five years and
adolescents in families with a tuberculous
background, especially when living with
tuberculous individuals.
3. The procedure might be expected to
be beneficial in adults who had had tuber-
culosis, in tuberculous subjects in order to
avoid relapses, as well as in silicotic and
siderotic miners.
4. Chemoprophylaxis should be integrat-
ed with antituberculosis vaccination and
nonspecific prophylaxis which still are the
bases of the prevention of tuberculosis.
RESUMEN

1. Las terneras sometidas a quimioprofilaxis después de una infección primaria resultante de exposición a vacas tuberculosas, adquirieron una inmunidad que las protegió contra una reinfección masiva con bacilo Tb bovino. Esta inmunidad corresponde a la que se obtiene por la vacuna BCG y se mantiene aún si la reinfección ocurre seis meses después de interrumpida la quimioprofilaxis.

2. En Italia se han llevado a cabo intentos de quimioprofilaxis en seres humanos en gran escala, desde Abril de 1956. La quimioprofilaxis se ha empleado en grupos escogidos expuestos a la tuberculosis en los hogares o en las escuelas. Estos grupos incluyen a todos los niños tuberculinos-positivos menores de 5 años, y los adolescentes en familias en que hay tuberculosos, especialmente cuando viven con ellos.

3. Podría esperarse que el procedimiento fuera benefico para los adultos que han tenido tuberculosis, en los tuberculosos para evitar recádas, así como en silicosis y enfermos con siderosis.

4. La quimioprofilaxis debe integrarse con la vacunación antituberculosa y con la profilaxis no específica que son las bases aún de la prevención de la tuberculosis.

RÉSUMÉ

1. Les veaux soumis à la chimiothérapiée avec isoniazid après l'infection primaire provoquée par la contagion de vaches tuberculeuses ont acquis une immunité, qui les a protégés contre une nouvelle infection massive par voie parentérale provoquée par des bacilles tuberculeux de type bovin. Cette immunité est équivalente à celle que l'on obtient avec le B.C.G. et persiste même lorsque la nouvelle infection a lieu six mois après la fin de la chimiothérapiée.

2. En Italie les recherches sur la chimiothérapiée ont été effectuées à large échelle sur les hommes dès avril 1956. La chimiothérapiée a été appliquée à des groupes sélectionnés de sujets exposés au danger de la contagion dans les familles et dans les écoles. Ces groupes de personnes comprennent tous les enfants de moins de cinq ans dont la cuti-réaction était positive et les adolescents de familles ou existait un terrain constitutionnel prédisposé, en particulier lorsqu'il s'agissait d'individus vivant avec des maladies tuberculeuses.

3. Il faut attendre un résultat également favorable chez les adultes qui ont souffert de tuberculose, chez les tuberculeux pouvant avoir des rechutes, ainsi que chez les malades atteints de silicose et chez les mineurs travaillant dans les mines de fer.

4. La chimiothérapiée devrait être effectuée à côté de la vaccination antituberculeuse et de la prophylaxie non spécifique, que constituent encore an jour d'ici les bases de la prophylaxie antituberculeuse.

ZUSAMMENFASSUNG

1. Nach einer Primärinfektion infolge Exposition gegenüber tuberkulösen Kühen erwarben Kälber, die einer Chemoprophylaxe unterworfen worden waren, eine Immunität, die sie gegen eine massive parenterale Reinfektion mit bovinen Tuberkelbazillen schütze. Diese Immunität korrespondiert mit der durch die BCG-Impfung erreichten und besteht auch dann, wenn die Reinfektion 6 Monate nach Beendigung der Chemoprophylaxe auftritt.


3. Dieses Vorgehen kann man auch als nützlich bei Erwachsenen voraussetzen, die eine Tuberkulose gehabt haben, bei tuberkulösen Personen zur Vermeidung von Rückfällen, ebenso wie bei Bergleuten mit Silikose und Siderose.