

EVALUATION OF ISONIAZID AS A PROPHYLAXIS
AGAINST PROGRESSIVE MASSIVE FIBROSIS

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I. Objective and Background

Miners pneumoconiosis represents the main problem of occupational pathology in a great part of Yugoslavia, particularly because of the accompanying diseases (1,2,3). Pneumoconioses are complicated with tuberculosis in 15-28% and specially in advanced cases this percentage increases to 65% (4).

Studies conducted in the U.S.A. among persons at risk treated prophylactically with isoniazid at 5 mg. per kg. of body weight per day for a period of one-year reduced the incidence of tuberculosis over a five-year period by about 50% (Amer. Rev. of Resp. Diseases, Vol. 85, No. 6, June 1962; Vol. 88, No. 2, August 1963; Vol. 85, No. 4, April 1962; New England Journal of Medicine, Vol. 265, October 1961, Pp. 713-721). It is believed by many authors that in most cases complicated pneumoconiosis (progressive massive fibrosis (PMF)) is the result of a tuberculous infection.

To date controlled experiments on the effect of isoniazid in preventing complicated pneumoconioses have not been reported in the literature. Only some preliminary communications were published (5,6,7). P. Galy, et al (7) treated 19 patients with INH (300-500 mg. per day), and 23 others with Streptomycine, or PAS or Trecator+Viocine. Thirty-five of them had not progressed to PMF, while seven were complicated with tuberculosis. Some attempts were made with BCG vaccine (8,9). The role of tuberculin sensitivity in coal miners with pneumoconiosis was studied (10).

We decided to do a study with the objective to determine to what extent the prophylactical administration of isoniazid can prevent complications in a group of men with pneumoconiosis whose X-rays were initially negative for tuberculosis. If it could be proved that isoniazid materially decreased the incidence of complicated pneumoconiosis

an important step toward the alleviation of the most disabling aspects of coal dust disease would be possible. Because of a relatively high incidence of tuberculosis among Yugoslav miners there was an opportunity for a study economically not feasible in the United States of America. The data available in Yugoslavia indicate that it might be anticipated that for a group of X-ray category 2 and 3 of pneumoconiosis cases (1958 ILO classification) a great percent would develop complications within a five-year period. If the prophylactical administration of isoniazid for a one-year period is capable of reducing this incidence by as little as 25%, a study of 400 pneumoconiotics over a five-year period, divided at random into two groups, one given isoniazid and the other a placebo, would produce a statistically significant difference in the incidence of complicated pneumoconiosis. To accommodate dropouts this number was increased to 250 in each of the two groups.

II. Description of Research Plan

A group of 529 male workers from mines in Serbia, Crna Gora, Macdeonia, Bosnia, and Herzegovina who had pneumoconiosis of categories 2 and 3 without radiographic evidence of tuberculosis, and who were tuberculin positive was studied. Initially tuberculin tests and 35 cm X 35 cm chest X-rays were done on the entire group. The group was then stratified by age and X-ray classification, and within these categories, divided at random into two groups with 269 miners in one group and 260 in the other one. One group was administered isoniazid in a dosage of 5 mg. per kg. of body weight per day for a one-year period. In the same period the second group was administered a placebo indistinguishable (without chemical analysis) from the isoniazid tablets.

In order to choose the necessary number of cases with pure noncomplicated pneumoconiosis of categories 2 and 3 a great number of cardlists of inpatients and outpatients was searched (about 3500). Workers examined in the field and in mines periodically according to law were listed, too. Then a tour of mines was made in order to check whether the workers eligible for the experiment were alive and where they were living. The exact addresses were taken, the last diagnosis checked, and in the case of complicated pneumoconiosis they were eliminated. At last, the miners chosen in the abovementioned manner were X-rayed so that a firm choice of patients with pneumoconiosis of categories 2 and 3 without radiographic evidence of tuberculosis would definitely and undoubtedly be selected. At the same time the tuberculin test was made by PPD RTV₂₃ according to Mantou. The X-raying and tuberculin testing were performed under the

same condition, i.e., the X-raying was done using the same type of roentgen-apparatus, with the same elements, by one and the same operator. The tuberculin test was also performed by the same person, while the skin reaction was interpreted by the same doctor. Patients with a induration diameter of at least 5 mm were considered to have a positive tuberculin reaction. Other skin changes (erythema, bulla, vesicula, etc.) were recorded. X-ray films were read independently by three doctors who neither had any data about the X-rayed person, about his previous rentgenogram nor had they knowledge of whether the patient was receiving isoniazid or placebo. In order to be able to select 500 persons necessary for the experiment more than 1000 persons had to be examined. From the stratified sample the group for isoniazid was chosen at random. The average age of the treated group is 44.4 years and of the control 47.0 years.

After that, points for giving tablets were established. For nine mines (metal and coal) 22 points were organized taking care of the vicinity of the working place or domicile of ex-miners, or the possibility of engaging medical staff from health services to give tablets on the spot. The distribution of the daily dose of the drugs was performed by medical technicians or nurses from the health service in the mine or domicile. In one case it was a person from the safety service in the mine. This person did this at the entrance of the mine thus being able to gather people from both shifts. On the day of rest it was the responsibility of the patients to take the drugs at home by themselves. The persons distributing the drugs were controlled by the physician once or twice a week, and by the Principal Investigator or his Deputy once monthly. It was proved that the taking of drugs was regular owing not only to the efforts of the engaged persons, but more to the previous successful informing of the pneumoconiotics of the significance of taking the drugs as a prophylactic procedure. Besides, there were no troubles in the digestive system except in sporadic cases, therefore, the success was nearly complete.

| MINE | No. Persons In Experiment | | | No. of Points | Start |
|--------------|------------------------------|------------|------------|------------------|------------|
| | INH | Placebo | | | |
| Stolice | 38 | 22 | 16 | 3 | Oct. 1966 |
| Zajaca | 68 | 26 | 42 | 3 | Oct. 1966 |
| Sase | 24 | 12 | 12 | 1 | Nov. 1966 |
| Lece | 51 | 35 | 16 | 3 | Dec. 1966 |
| Vrska Cuka | 55 | 30 | 25 | 3 | Sept. 1967 |
| Bor | 31 | 20 | 11 | 2 | Sept. 1967 |
| S. Stijena | 50 | 20 | 30 | 2 | Nov. 1967 |
| Kisnica | 42 | 20 | 22 | 1 | Nov. 1967 |
| Zletovo | 170 | 84 | 86 | 4 | Dec. 1967 |
| Total | 525 | 269 | 260 | 22 | |

DISTRIBUTION OF PNEUMOCONIOTICS BY AGE

| AGE | Pneumoconiosis Category (ILO 1958) | | | | | | | |
|--------------|------------------------------------|------------|-----------|-----------|------------|--------------|------------|--------------|
| | Cat. 2 | | Cat. 3 | | All Men | | | % |
| | INH | Placebo | INH | Placebo | INH | % | Placebo | |
| 21-30 | 3 | 3 | - | - | 3 | 1.1 | 3 | 1.2 |
| 31-40 | 74 | 54 | 29 | 9 | 103 | 37.5 | 63 | 25.1 |
| 41-50 | 64 | 49 | 28 | 45 | 92 | 33.4 | 94 | 37.4 |
| 51-60 | 42 | 40 | 17 | 20 | 59 | 21.5 | 60 | 23.9 |
| 60 | 10 | 19 | 8 | 12 | 18 | 6.5 | 31 | 12.4 |
| Total | 193 | 165 | 82 | 86 | 275 | 100.0 | 251 | 100.0 |

| MINE | Start | | First Progr. | Control | |
|------------|-------|---------|-----------------|---------|------|
| | INH | Placebo | | Tb | Died |
| Stolice | 22 | 16 | | | |
| Zajaca | 26 | 42 | | | 1 |
| Sase | 12 | 12 | 1 | | 1 |
| Lece | 35 | 16 | 1 | | |
| Vrska Cuka | 30 | 25 | 1 | | |
| Bor | 20 | 11 | | | |
| S. Stijena | 20 | 30 | 1 | 1 | |
| Kisnica | 20 | 22 | | (2) | 1 |
| Zletovo | 84 | 86 | 3 | 2 | 1 |

After a one-year period X-ray examinations as well as tuberculin tests in both the experimental and control group were performed. This was done under the same conditions as in the start, i.e., with the same type of roentgen-apparatus, with the same elements, and same persons. The films were read independently by the same doctors and again they did not have any data about the X-rayed persons. The film readings were done on three occasions.

Changes which indicated a possible tuberculous infection were observed in four cases. In seven persons a progression of pneumoconiosis was found, and in two of them there were signs of a tuberculous infection. Three of the pneumoconiotics died; one was a victim of an accident, one committed suicide and one died. We are carrying on an inquiry regarding this last person in order to find out the cause of his death.

The first control was completed at all points at the end of 1968 because the last group of persons could start to take isoniazid or placebo at the end of 1967. There were many reasons why the points could not be established simultaneously in all places: in two miners we had to wait for the roentgen-apparatus to be installed which had to be of the same type used in the other places; small mines with a small number of non-complicated pneumoconiosis; different systems of medical care, i.e., a different health service organization from state to state, even from area to area which required many contacts with a greater number of physicians; health services; mine boards, etc. We were aware that the success of this work would depend on the good knowledge of people and medical personnel of the aims of the experiment and on their acceptance of this work. Besides, the main reason for a successive start was our plan to have by all means the same technical personnel for each part of the work. Some times there were difficulties with road communications in the mine area or settlements (during wintertime) where miners and ex-miners live.

The distribution of the drugs itself was conducted in blind so that neither the physicians nor the patients or distributors knew what the patients received. The labels on the bottles were identical, with the only difference that on the labels of one sort of pills a small misprint was made.

It was anticipated by the contract that this would be the last year of activity on the project. Meanwhile, because of reasons mentioned above this activity has not been finished and no final report of the obtained results is ready.

Namely, since the points could not be established simultaneously the last group of miners started to take isoniazid or placebo at the end of 1967. This means that the last control (examinations) will have to be done at the end of 1972. The difficulties which arose in organizing of this complex experiment were reported in previous reports. Then an extension of the time-limit for completing the experiment was provided.

It was observed that it was a pity we had no financial means for an every year control which would help to keep better contacts with the persons participating in the experiment. Therefore, since a long interval was made between the previous and next control, it should surely be expected that a number of persons would be dropped from the control. For that reason it should be necessary to undertake a new action to get people acquainted with this work in order to provide a regathering of the miners for the next control. In the meantime a reorganization of the health services has taken place, some physicians have left the mines, many managing bodies have changed. All that, requires a re-engagement and intensified efforts of the Institute team in performing the project. In spite of this situation we had regular contacts with the people in the experiment through letters or in person, we were interested in their social problems, state of health, and helping them to realize benefits according to the law, etc.

III. Further Activity

If it would be possible to realize an extension of the work by introducing respiratory function tests, gas analyses, allergen tests, bacteriologic and cytologic sputum analyses, the time-limit would be prolonged. New financial sources would be needed for that. If it would not be possible, the further course of activity would be as follows: radiography, tomography wherever needed, sputum analyses in the cases where evidence of tuberculosis developed. All results would be elaborated statistically.

This report represents only a preliminary communication. Any suggestions and proposals regarding the further activity would be gratefully accepted.

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DISCUSSION AFTER DR. POPOVIC'S PAPER:

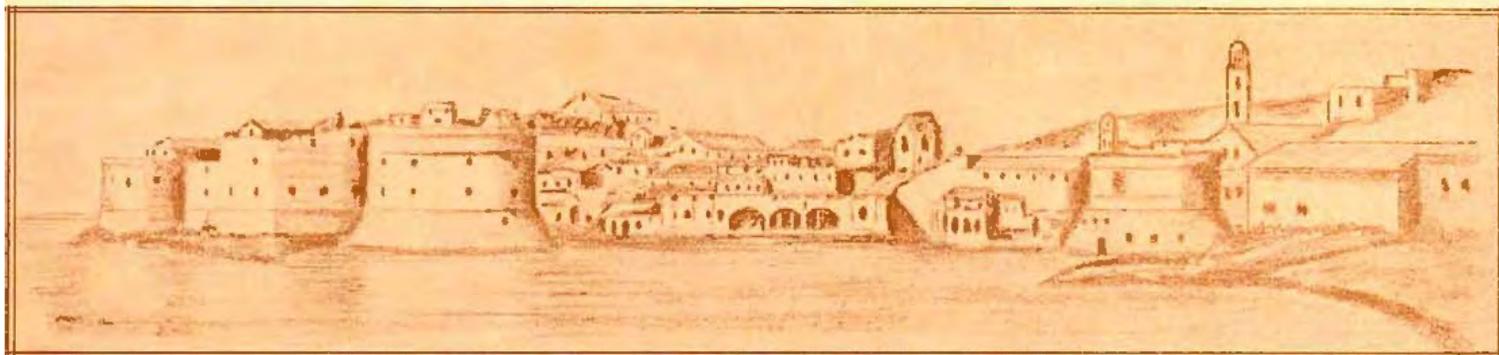
Dr. Lainhart:

Did you have any reaction to either drug -- either the isoniazid or placebo on the part of the individuals taking part in this study? Did any of them have gastroenteritis or actually have to stop either drug?

Dr. Popovic:

Yes, they had some troubles but only sporadic ones. We explained to them to have some cakes or some bread, not to take isoniazid on an empty stomach. Of course, they did not know which tablets they received and after that troubles disappeared. That meant, we practically succeeded in regular taking of the drugs. We don't know for the present time if the seven cases of PMF and four cases of suspicious TB received izoniazid or placebo? We will know it in five years.

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