The Therapy of Pulmonary Tuberculosis and Its complications by Thiosemicarbazone*

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Domagk is considered the pioneer of chemotherapy in tuberculosis with thiosemicarbazones. He studied, in cooperation with his collaborators, a large number of thiosemicarbazones developed by the chemists Behnisch, Mietzsch and Schmidt, has found that the 4-acetaminobenzoic-thiosemicarbazone was the most efficacious substance against the tubercle bacillus. This compound, according to Domagk's researches on cultures of tubercle bacillus of the human type on egg culture medium containing p-aminobenzoic acid, exerts a marked inhibitory effect on the growth of tubercle bacillus at 1:300,000 solution, whereas streptomycin under the same conditions, shows an inhibition value at from 1:50,000 to 1:100,000 and PAS at 1:5,000. The in vivo effect has been confirmed by Domagk in experimental tuberculosis in guinea pigs and rabbits.

The clinical application in humans of this drug began in Germany in 1947. Many thousands of patients suffering from various forms of pulmonary and extrapulmonary tuberculosis have been subjected to this treatment.

Clinical Material: 37 patients all female, aged 19-65 years

Appearance of illness prior to treatment: In six cases recent, one to six months; in eight cases, one year; in seven cases, two years; in five cases, three years; in 11 cases, four to eight years.

Temperature prior to treatment: In 18 cases high fever, maximum 40 degrees C.; in 16 cases moderate, maximum 38 degrees C.; in three cases normal temperature.

Clinical classification of pulmonary tuberculosis: In 34 cases progressive form, in three cases stationary.

Pathologic classification from the roentgenogram of the pulmonary process: In 15 cases mixed, with predominance of the exudative type; in 22 cases mixed, with predominance of the productive type.

Cavitary: Unilateral or bilateral in 35 cases.

Other forms of tuberculosis: Tuberculous laryngitis in nine, with intense local clinical symptoms and laryngologic findings ranging from oedema to ulcerations. Tuberculous bronchitis in three, presenting clinically excessive frequent spasmodic cough, with bronchoscopic findings consisting of ulcerated lesions located in the right main bronchus and the bronchi of the upper right and upper left lobes. Tuberculous enteritis in one case, present-

*Presented before the Medical Association, Athens, Greece, March 22, 1952.
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ing the full clinical picture of intestinal tuberculosis but not verified by x-ray film due to the severity of the patients condition.

Dosage: It is apparent from this study that the daily dosage of 150 to 200 mg. is sufficient to act therapeutically and to be fairly tolerable to almost all patients. This daily dosage is reached progressively by administration of 25 to 50 mg. daily during the first week, 100 mg. the second week, 150 mg. the third week and finally 200 mg. The rhythm of the dosage necessitates special attention for each patient. In severe cases with intense toxic symptoms, according to the personal advice of Domagk, the initial dose must be 12.5 mg. (half tablet) and the dose of 150 mg. must be reached slowly having as criterion for the increase of the dosage both the therapeutic effect of the drug and its tolerance by the body; because should important toxic reactions arise, treatment must be discontinued promptly for a few days. When the effect of the medication is beneficial and the drug is well tolerated, treatment should be continued for months. The longest period for our patients who received the drug was over 223 days, with a maximum total dosage of 28 Gm.

Laboratory examination: During the course of treatment, in addition to the usual clinical observation the following laboratory examinations were performed monthly: (1) examination of the sputum smear or of the fasting gastric contents for tubercle bacillus; (2) chest roentgenogram; (3) complete blood count; (4) erythrocyte sedimentation rate determination; (5) urinalyses. As regards the chemical control of the hepatic function, besides the urobilinogen excretion in urine, the thymol turbidity and cephalin flocculation examinations have been made. Also the plasma protein content and the albumin-globulin ratio have been determined by laboratory tests prior and after end of treatment.

Results

Clinical observations: Improvement in seven cases. No change in 25 and worsening in one. Interruption of treatment in four. The clinical improvement in the seven above mentioned cases consisted of apyrexia, reduction of cough, decreased expectoration, disappearance of tachycardia and night sweats, and gain in weight. This symptomatic improvement does not appear immediately after the first days of treatment, as observed during streptomycin therapy, but after 10 to 30 days from the starting of chemotherapy. This slow effect, observed also by other authors is why the use of thiosemicarbazone is counterindicated for the treatment of miliary tuberculosis.

In all the cases of laryngeal tuberculosis an evident result was noted with complete disappearance of voice changes and dysphagia. The symptoms usually responded rapidly within the first 10 days of treatment and were accompanied by improvement of laryngeal lesions. The response of treatment of laryngitis was greater when it was followed by improvement in the pulmonary process.

In the three cases of tuberculous bronchitis a marked reduction of cough was noted. The bronchoscopic examination revealed from simple improvement to healing of endobronchial lesions.
In the one case of tuberculous enteritis the clinical improvement was apparent and the persistent pain and diarrhea showed an evident regression.

**Laboratory data:** Sedimentation rate of erythrocytes: In all cases with clinical improvement a fall of the erythrocyte sedimentation rate, sometimes considerable, was observed.

Sputum: Conversion from positive to negative for acid-fast bacilli occurred in four cases. The negativity persists for three to four months.

X-ray changes: In five cases of the seven showing clinical betterment, improvement in the roentgenograms was also observed consisting of diminution and clearing of the perifocal reaction. The radiologic improvement was not so clearly evident as in similar streptomycin-treated cases. Clinical and radiological improvements were noted in relatively recent tuberculosis with predominance of the exudative type and with intense perifocal reactions. No changes were observed in forms of chronic fibro-ulcerative tuberculosis.

**Toxic reactions:** Digestive system: The most frequent symptoms were from the stomach during the conteben therapy such as anorexia, sometimes intense, discomfort and pain in the epigastric region, anorexia and in some cases vomiting, which symptoms may disappear with the continuing of treatment, but when they persist and vertigo and headache are added to them, it is necessary to discontinue the medication. Treatment had to be interrupted with the appearance of the above mentioned symptoms in four cases. Skin and the conjunctiva: In eight patients conjunctivitis developed, rather uncomfortable, and generalized exanths pruritic, macular or erythematous or pruritus without exanthem. These toxic manifestations subsided by reducing the dosage and by the administration of antihistaminic drugs or after temporary interruption of the treatment.

**Blood:** Moderate hypochromic, haemolitic anaemia developed in seven cases. However, treatment was continued with reduced dosages and during the treatment the erythrocyte count became gradually almost normal. In two a fall of the total leucocyte count below 5,000 per cu.mm. was observed and after discontinuation of treatment the leucocyte count became shortly normal; but no true picture of granulocytopenia was noted, in spite of the opinion of some authors stating that this complication appears more often in women and is due to the toxic effects of the drug on the haematopoetic system. This complication, if it appears, is serious and necessitates immediate discontinuance of treatment.

**Liver:** In one case subicteric skin changes with vomiting and pain in the right hypochondric region was noted and disappeared very slowly when the medication was interrupted. In this case and in another the thymol turbidity was higher than five units. We do not believe that the daily dosage of 150 to 200 mg. is hepatotoxic. This opinion was confirmed by laboratory tests of the hepatic function made in most of the cases. The plasma protein content and the albumin-globulin ratio were not perceptibly changed.

**Kidneys:** Albuminuria was present in four cases without other findings.
Rather significant haematuria was found in one and in two aggravation of the preexisting pyelocystitis.

SUMMARY
The use of 4-acetylanobenzaldehyde-thiosemicarbazone in the treatment of pulmonary tuberculosis, applied particularly in the recent form with exudative lesions and in the acute relapsing forms, exerts some beneficial effect, particularly on clinical symptoms, exudative processes and perifocal reactions, little effect or none against chronic pulmonary tuberculosis.

The therapeutic efficacy of this drug is evident and clear in laryngeal as also in tuberculous bronchitis and enteritis.

The administration of the drug is not indicated for the treatment of miliary and meningeal tuberculosis because its effect is slow. It has not yet been fully investigated if thiosemicarbazone resistant bacilli developed during the treatment. Possibly the emergence of such resistant bacilli is slow. No conclusions have been drawn either if the combination of the drug with streptomycin delays the appearance of streptomycin-resistant bacilli.

The dosage for each patient should be individualized. As it is apparent from the present study the dosage of 150 to 200 mg. daily is therapeutically feasible and fairly well tolerated.

The toxicity of the drug with the reported dosages is not significant. In spite of this the treated patients should be under medical observation.

RESUMEN
El uso de la 4-acetilaminobenzaldeido-tiosemicarbazona en el tratamiento de la tuberculosis pulmonar aplicada particularmente en las formas recientes con lesiones exudativas y en las recaidas agudas ejerce algún efecto benéfico especialmente en los síntomas, en las reacciones exudativas y perifocales, pero ningún efecto o muy poco sobre la tuberculosis pulmonar crónica.

La eficacia terapéutica de esta droga es evidente y clara en la tuberculosis laringea, en la bronquitis tuberculosa y en la enteritis de ese origen.

La administración de esta droga no está indicada en las formas miliares y meníngeas porque su efecto es lento.

No se ha investigado aún si se desarrollan bacilos resistentes a la tiosemicarbazona durante el tratamiento. Posiblemente la aparición de tales formas resistentes, es lenta. No se ha llegado a conclusiones respecto de si la combinación con estreptomicina retarda la aparición de resistencia a esta última.

La dosificación en cada caso, debe ser individual. Es evidente, según este estudio que la dosis de 150 a 200 miligramos al día es práctica terapéuticamente y bastante bien tolerada.

La toxicidad de la droga con las dosis referidas, no es significante. A pesar de esto, los enfermos tratados deben servigilados.

RESUME
Le 4-acétylaminoenbenzaldehyde-thiosémicarbazone, utilisé dans le traitement de la tuberculose pulmonaire, surtout dans les formes récentes à lésions exsudatives, et dans les rechutes à caractère aigu, à un effet favo-
rable, spécialement sur les symptômes cliniques, les processus exsudatifs, et les réactions périfocales. Par contre, l’effet est de peu d’importance ou nul sur la tuberculose pulmonaire chronique.

L’efficacité thérapeutique de cette drogue est évidente dans les atteintes laryngées, aussi bien que dans la bronchite et l’entérite tuberculose.

L’administration du produit n’est pas indiquée dans le traitement de la tuberculose millaire et méningée, parce que son effet est lent. On n’a pas encore trouvé si une résistance au produit pouvait se développer au cours du traitement. Mais il est possible que l’apparition de bacilles résistants soit lente. On ne sait pas encore si l’association de ce produit à la streptomycine retarde l’apparition de la streptomycino-résistance.

La dose doit être adaptée à chaque malade. Il résulte de l’étude actuelle que la dose de 150 à 200 mmgr. par jour est efficace, et est bien tolérée.

Le produit, administré à de telles doses, ne se montre pratiquement pas toxique. Néanmoins, les malades en cours de traitement doivent rester sous contrôle médical strict.

REFERENCES
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