No. 7] 391

88. The Management of Drug Resistant Bacilli in the Chemotherapy of Pulmonary Tuberculosis

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It is well known that the most important hindrance in the chemotherapy of pulmonary tuberculosis is the appearance of tubercle bacilli resistant to anti-tuberculous drugs. The resistance against SM has been pretty well studied and is sometimes accompanied by dependency or enhancement. But it occurs very rarely and one can not make use of it in the management of resistant tubercle bacilli. P. J. Coletsos 1) thinks as Garrod 2) already reported that one should not depend upon making use of this phenomenon to cause tubercle bacilli to disappear from the host. Garrod's opinion is this: “It seems highly improbable that converting the organism to dependence and then starving it by withdrawal of the drug will be found a successful method of treatment. Bacterial populations in which such changes are occurring are highly heterogeneous, including organisms possessing varying degrees of simple resistance and some which are still sensitive, as well as dependent cells”. Concerning resistance of tubercle bacilli against INH there are many studies, such as, for instance, with regard to its catalytic ferment and its diminished virulence etc., but about its dependency little is known.

It is possible to find that long term treatment simultaneously with INH and SM causes tubercle bacilli in patients so to degenerate that they sometimes tentatively disappear upon withdrawal of drugs. If not entirely, they are so degenerated that they are very sensitive to sulfa drugs. Sulfa drugs per se are not strong enough for non-degenerated tubercle bacilli. Practical use can be made of this fact in the treatment of cases of pulmonary tuberculosis whose tubercle bacilli have developed resistance against INH and SM.

We reported 3)-6) already that the treatment of cavitary pulmonary tuberculosis with PAS 10 g daily, SM 0.5-1 g and INH 150-200 mg twice a week for one and a half years makes tuberculous cavities cicatrize or fibrotic as well as cleaned out, because this regimen first heals all the tuberculous affection of draining bronchi and keeps them open. Sometimes a small caseoma under 0.5 mm in diameter may remain in the course of the healing of cavities but this small inspissated caseoma can be considered safe if the patients have received chemo-
therapy long enough, for the small caseoma then contains no living tubercle bacilli. This regimen is a little different from the triple drug regimen being used in foreign countries: it contains less INH, i.e. about one third of the quantity of the latter. But even in this regimen drug resistant tubercle bacilli can appear in about 10 to 20 per cent of the cases after a treatment of over 6 months. Under these circumstances we make our regimen stronger; namely we give PAS 10 g daily, SM 1 g and INH 200 mg every other day. If this regimen causes no improvement and tubercle bacilli are being excreted in the sputum we administer three drugs daily for 3 months. When tubercle bacilli in the sputum do not disappear under this regimen the degree of resistance may become stronger. Then we discontinue INH and SM suddenly, and give PAS and a sulfa drug daily for 3 to 6 months. Generally the tubercle bacilli in the sputum gradually decrease, sometimes suddenly; X-ray findings improve, showing cavities either diminished or sometimes gone. When the improvement is not sufficient we administer three drugs, PAS, SM, and INH daily again for 2 to 3 months and after that PAS and a sulfa drug daily. This procedure can be repeated many times, if necessary.

Two and a half years ago we started treating in this way over 120 cases of pulmonary tuberculosis with resistant tubercle bacilli. About one third of them are resection—or thoracoplasty—failure cases. We have a lot of such patients who were sent from other sanatoriums or other hospitals. In 50 out of 120 cases the treatment was successful, that is, the tubercle bacilli in the sputum disappeared, and the cavities cicatrized or became fibrotic.

That the procedure of this treatment has an intimate relation to the dependency of the tubercle bacilli on the drug can be reasoned out as follows:

1) Tubercle bacilli in the sputum decrease or disappear upon withdrawal of the drug, even though temporarily.

2) After tubercle bacilli have decreased or disappeared upon treatment with PAS and the sulfa drug, they sometimes reappear abundantly in the control tube as well as in the tube with the drug, when INH and SM are given again.

3) Sometimes tubercle bacilli grow only in the tubes which contain the drug, while the control tube shows no growth.

The sulfa drugs we are using are 3,4-dimethyl-5-sulfanilamidooxazol (Japanese trade name, thiasin; Roche trade name, gantrisin); \(N_1\)(-2,6-dimethyl-4-pyrimidyl) sulfanilamide-(Japanese trade name, domian); sulfadiazine, and as sulfone drug, promizole.

Three case histories will be cited.

Case 1: R. S., age 37, female, nurse. In 1950 X-ray examination
showed a shadow in the lung. She took a rest for one year. From August, 1953 she began to cough and took INH 100–200 mg daily and SM 1 g twice a week. By March, 1954 she had recovered and was rehabilitated but the cough remained. In October, 1957 she was admitted to our Hospital. Our triple drug regimen was administered for 8 months. Her sputum smear was G VI, on culture resistant to SM 10γ and INH 100γ. On June 20 her right upper lobe was resected. After that no tubercle bacilli showed in her sputum for 2 months. Then her sputum became G III–G VI, resistant to SM 10γ, PAS 1γ, and INH 100γ. X-ray film on admission showed a cavity in the right upper lobe. After operation a bronchial fistula was revealed by bronchography. She was administered PAS and SM twice a week for 4 months. Next the triple drug regimen was given every other day for one month and the triple drugs daily for 2 months. The regimen was discontinued and PAS 10 g and thiasin 3.0 g daily were given. Her sputum examination on March 16, a half month later, showed on smear G II, on culture control tube negative and tubes with INH 0.05γ and 0.1γ positive and all other tubes negative. One month later all tubes with and without drugs were negative on culture. The examination on March 16 showed that tubercle bacilli could grow only in the tubes which contain INH. This was a sign of the tubercle bacilli in her sputum becoming dependent on INH.

Case 2: Y. N., age 17, female, high school student. In November, 1953 she complained of a cough and was diagnosed as having pulmonary tuberculosis. She received pneumothorax for one year and three drugs

Fig. 1. Y. N. (Case 2)
Tomogram taken on July 16, 1958
Cavity of 15×20 mm in size was visible in the right upper lobe.

Fig. 2. Y. N. (Case 2)
Tomogram of April 17, 1959
No more cavity is visible. It shows only the indication of fibrosis.
for 2 years and 7 months. In July, 1958 she was admitted to our Hospital. At that time her sputum was G VII, resistance to SM 10γ+, PAS 1γ+, and INH 10γ+. X-ray film showed a cavity measuring 15×20 mm in size. One and a half months later, August 31, the triple drug regimen was stopped. Her sputum examination on September 16 showed G IV but the culture negative on control tube as well as the tube with drugs. Her sputum examination on October 14 showed G O and culture negative. On November 1 on smear G III, on culture control tube +++, tube with 10γ SM +++, tube with PAS 10γ+, and tube with INH 0.1γ +++, 0.5γ +++, 0.10γ +++, and 100γ −. She was given thiasin alone 3 g daily for one month. From November 1 PAS and thiasin daily were given for one month. Her sputum examination on December 3 showed on smear G O, and on culture control tube +, tube with INH 0.05γ + and 0.1γ −. From January 6 the three drugs were administered daily for 2 months and a half. Thereafter PAS daily and thiasin daily instead of three drugs were given. Her sputum examinations of April 2, 14, and 30 G O and all tubes were negative on culture. The remarkable findings in this case were these: tubercle bacilli disappeared temporarily after the stoppage of the three drug chemotherapy on smear as well as culture and reappeared again. X-ray film taken after 10 months showed that the cavity had disappeared, leaving only the indication of fibrosis.

Case 3: K. M., age 56, male, physician. At the age of 46 years he developed a cough, had bloody sputum, and took PAS alone. At 52 years of age he complained of bloody sputum and short breath, and was admitted to a hospital. The three drug chemotherapy was given for one year and 2 months and then PAS and 2 g of pyrazinamide were daily given for 6 months. On April 1, 1958 he was admitted to our Hospital. The X-ray film at that time showed a cavity measuring 30×30 mm in the left side and a cavity, 15×15 mm in the right side. His sputum examination was on smear G VIII−X, on culture resistant to SM 1000γ, to PAS sensitive, and incompletely resistant to INH 0.5γ. The triple drug regimen was given daily for one month and a half and was stopped because of disturbance of the ears, and then PAS 10 g daily and INH 300 mg daily were given for one month and a half and discontinued. Next PAS 10 g and thiasin 3 g daily were continued for 6 months and a half. The tubercle bacilli in his sputum decreased very slowly but 4 months later his sputum was negative on smear but positive on culture. Six months later it became G II and culture positive again. PAS 10 g, INH 300 mg, and SM 0.5 g were given daily for 3 weeks and the regimen was changed to the regimen with PAS 10 g daily and thiasin 3 g daily. His sputum examination
on February 19, twelve days after stoppage of the triple drug revealed abundant growth of tubercle bacilli on culture. On control tube ++++, tube with SM 1000 r + and tube with INH 0.1 r +, but after the treatment with PAS and thiasin for 2 months and a half all tubes

**Fig. 3. K. M. (Case 3)**  
Tomogram of the right lung taken on March 31, 1958  
A cavity of $15 \times 15$ mm in size in $S^2$ and two small caseomas in $S^{1+2}$ are visible.

**Fig. 4. K. M. (Case 3)**  
Tomogram of the right lung taken on July 23, 1958  
The cavity disappeared, instead of it a scar appeared. Tuberculomas in $S^{1+2}$ are cicatrized.

**Fig. 5. K. M. (Case 3)**  
Tomogram of the left side taken on March 31, 1958  
Cavity measuring $30 \times 30$ mm is found in $S^2$.

**Fig. 6. K. M. (Case 3)**  
Tomogram of the left side taken on March 6, 1959  
The cavity almost disappeared but quite a small slit is visible.
with and without drug were negative on culture. Thereafter all sputum examinations were negative for tubercle bacilli. Four months later the cavity in the right side disappeared and 6 months later the cavity in the left side diminished to quite a small one. What is remarkable in this case is that the tubercle bacilli in his sputum diminished very much by the use of PAS and thiasin but by addition of SM and INH they increased again; then disappeared by repetition of the regimen with PAS and thiasin.

References