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A M E R I C A N C O L L E G E O F
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Retreatment of Drug Resistant Tuberculosis at Battey State Hospital

RAYMOND F. CORPE, M.D., F.C.C.P.* AND FRANK A. BLALOCK, M.D.**

Rome, Georgia

INTRODUCTION

PROPER INITIAL CHEMOTHERAPY IN BATtey State Hospital results in a reversal of infectiousness in over 95 per cent of all advanced cavitary cases of tuberculosis. Patients continuing to excrete tubercle bacilli will develop organisms resistant to those drugs employed. Past periodic sampling and now routine observation of the sensitivity and resistance status of all admissions points out that primary drug resistance is not on the increase in Georgia.

The United States Public Health Service¹ reports "Of the strains tested for 1961-62 admissions, 1.6 per cent were resistant to isoniazid (1+ growth in 0.2 $\mu\text{g./ml.}$), 28 per cent were resistant to streptomycin (3+ growth in 10 $\mu\text{g./ml.}$), and 0.8 per cent were resistant to para-aminosalicylic acid (1+ growth in 10 $\mu\text{g./ml.}$). Rates at least as high were found for each drug between 1952 and 1960, indicating that there has been no significant increase in primary drug resistance during the past decade. The absence of change must indicate that the primary drug resistance detected today in the United States is due, not to infection by persons whose bacilli became resistant during treatment, but to the presence of naturally resistant organisms." While this latter sentence may be true in part, we believe some of our primary resistance infections have been person-to-person transmitted from a secondarily resistant source, that is from treatment failure cases. Hobby, *et al.*² also report the low prevalence of primary drug resistance in the United States.

Prior to March 1, 1962 streptomycin, isoniazid, para-aminosalicylic acid, viomycin, pyrazinamide and cycloserine had been readily available for clinical use in many

varying regimens in our hospital. Battey Hospital has continuously participated in the United States Public Health Service controlled drug studies from their beginning in the early 1950's. A progressive surgical program has also been in effect during this period of time. Nevertheless, we had accumulated a hard core of drug-resistant treatment failure cases. From our own experiences, we knew that the addition of one new drug at a time was doomed mostly to failure. We are profound believers in initial drug regimens containing three or four drugs; either daily streptomycin, isoniazid and para-aminosalicylic acid or regimens of daily streptomycin and pyrazinamide, alternating monthly with daily isoniazid and para-aminosalicylic acid for cavitary advanced tuberculosis.

Dr. Virgil Place of Lederle Laboratories agreed to furnish us their brand of ethambutol,^{3,4} which we planned to use as the anchor drug. Neither ethionamide nor kanamycin had ever been used among our treatment failure cases. We, therefore, had a minimum of three virgin drugs for retreatment purposes.

MATERIALS AND METHODS

Eligibility for admission to the study required patients to be treatment failures with a life expectancy of one year. Pre-study evaluation required liver, kidney, hematologic and neurologic clearance, including visual acuity testing, eyeground examinations and audiograms. Sensitivity studies were done for the three major drugs (streptomycin, isoniazid and para-aminosalicylic acid), plus five secondary drugs (viomycin, cycloserine, kanamycin, ethambutol and ethionamide).

A basic drug regimen of ethambutol (EMB), ethionamide (ETH), and isoni-

*Superintendent, Battey State Hospital.
**Chief, Clinical Research, Battey State Hospital.

TABLE 1—TREATMENT; DOSAGE SCHEDULE FOR DRUG RESISTANT STUDY

Hour	Isoniazid	Kanamycin	Ethambutol	Ethionamide	Cycloserine
8:00 a.m.	150 mg.			250-500 mg.	500 mg.
10:00 a.m.		15 mg./kg.			
12:00 noon	150 mg.		25 mg./kg.	250-500 mg.	500 mg.

azid (INH) was used to initiate therapy. If sensitivity existed for cycloserine (CS), viomycin (VIO), or pyrazinamide (PZA), these could be next added to the basic drug regimen on a selective basis, singly or in combination, or previously unused kanamycin (KM) could be added to aid in reversal of infectiousness or in an attempt to elevate the serum antimycobacterial titer (Table 1).

The period of time in this study dates from March 1, 1962 to September, 1964. One hundred seven (107) patients have been admitted to this study. Forty-seven (47) of the patients were white men, 13 were white women, 31 were colored men and 16 were colored women. Only two patients were under the age of 20; 14 were between the ages of 20 and 39; 62 were between the ages of 40 and 59; 28 were between the ages of 60 and 79, and one patient was over 80 (Table 2).

Twenty-four had been hospitalized less than three years, but more than one year, 29 had been hospitalized between three and five years, and 54 of them had been hospitalized over five years (Table 3).

Forty-three were not surgical candidates. Seventeen in the study were considered to be surgical candidates, but refused to accept the proposed surgery. Forty-seven of the 107 patients (44 per cent) were surgical failures. Ten had resections of less than a lobe, seven of them had had lobectomies, five of them had had lobectomies plus smaller parts of an additional lobe,

nine had had pneumonectomies, and 16 were thoracoplasty failures (Table 4).

Upon admission to the study, 85 of the patients were classified as far-advanced, 18 were moderately-advanced and four were classified as minimal.

The 107 patients were positive and drug-resistant upon entry into the study (Table 5). Forty-three were resistant to three major drugs plus two secondary drugs; 21 were resistant to two of three major drugs plus two secondary drugs; 18 were resistant to two of three major drugs plus one secondary drug; ten were resistant to three major drugs plus one secondary drug; six were resistant to two of three major drugs; three were resistant to two of three major drugs plus three secondary drugs; three were resistant to three major drugs plus three secondary drugs; two were resistant to three major drugs; and one patient was clinically resistant, that is, he had positive sputum and negative cultures.

The drug combinations utilized in this retreatment program are depicted in Table 6. The basic drug regimen consisted of ethambutol, ethionamide and isoniazid, even though pre-existing resistance to isoniazid was present. Specific antimycobacterial titers were run monthly on these patients. Additional drugs were added to the basic regimen if sputum conversion did not occur, or, in an attempt to elevate the specific antimycobacterial titer.

Three consecutive months of two negative sputum cultures per month were neces-

TABLE 2—AGE, RACE AND SEX

Age	WM	WF	CM	CF
Under 20	2	0	0	2
20-39	14	2	3	5
40-59	62	31	7	7
60-79	28	13	3	2
80 +	1	1	0	0
Total	107	47	13	16

TABLE 3—DURATION OF HOSPITALIZATION PRIOR TO THIS REGIMEN

	WM	WF	CM	CF
Less than 3 years	24	10	4	2
3-5 years	29	12	4	4
Over 5 years	54	25	5	10
Total	107	47	13	16

TABLE 4—STATUS IN REGARDS TO SURGERY

Non-surgical candidates	43
Refused surgery	17
Surgery failures	47
Total	107

sary to state that a patient had obtained reversal of infectiousness. Reversal of infectiousness was obtained in 90 (84 per cent) of the 107 patients (Table 7). With a new, vigorous therapeutic approach, 73 of the 90 patients showing reversal of infectiousness did so in the first four months.

It was our impression that these retreatment failure cases had resolved the majority of the reversible components of their disease on previous therapy. However, when we analyzed the results of therapy as judged by x-ray examination, we found that 24 revealed no change, 67 revealed slight improvement, and 16 revealed moderate improvement.

Eighty (75 per cent) of the patients were able to tolerate their drugs as prescribed (Table 8). Twenty-seven (25 per cent) had some degree of toxicity. Nineteen (18 per cent) had minor drug interruption. Six had ethambutol discontinued for a few days because of complaints referable to the eyes. Evaluation revealed that none of these six patients had drug toxicity and they were all continued on scheduled therapy. These actually should not be counted as minor toxicities, but they did have temporary drug interruption. Nine patients had ethionamide discontinued temporarily, a few days at a time, because of gastric intolerance. The six that had temporary kanamycin discontinuance had local tissue dis-

comfort. Because of this they were given a few days without intramuscular injections.

Eight (7 per cent) patients had permanent drug interruption. The four who had ethambutol discontinued permanently did not have any degree of permanent eye damage. All four in whom kanamycin was permanently discontinued had prior hearing loss. One had progression to deafness and the other three had hearing loss sufficient to stop therapy.

DATA, PURPOSE AND ANALYSIS

Data on age, race, sex, drug resistance, degree of tuberculosis, toxicity, drug treatments, months of previous hospitalization, surgery, x-ray changes, sputum conversion, degree of overall treatment result and monthly specific antimycobacterial titers from 107 patients, on computer print out sheets, were submitted to the Statistical Division of Lederle Laboratories for analysis. Miss Roberta Wilcox did the analysis.

We were interested in correlating sputum conversions with the many factors which could affect it, especially antimycobacterial titers. At each month of study, the effects on sputum of race, sex, age, previous months of hospitalization, toxicity, degree of tuberculosis, specific antimycobacterial titer, drug treatments, and months on drug were analyzed with the aid of a computer. In addition, the effects on the month of sputum conversion of race, sex, age, toxicity, degree of tuberculosis, months of previous hospitalization, and in the month in which sputum conversion occurred, the specific antimycobacterial titer and drug treatment along with the months on that drug

TABLE 5—PRE-STUDY DRUG SUSCEPTIBILITY DATA

Resistant to three major drugs, plus two secondary drugs	43
Resistant to two of three major drugs, plus two secondary drugs	21
Resistant to two of three major drugs, plus one secondary drug (PZA, VIO, CS)	18
Resistant to three major drugs, plus one secondary drug	10
Resistant to two of three major drugs (I, SM, PAS)	6
Resistant to two of three major drugs, plus three secondary drugs	3
Resistant to three major drugs, plus three secondary drugs	3
Resistant to three major drugs (I, SM, PAS)	2
Other—clinically resistant	1
Total	107

TABLE 6—DRUGS EMPLOYED IN TREATMENT AND CONVERSIONS

	No. Pts.	Conversions
Ethambutol, ethionamide and isoniazid	16	15
Ethambutol, ethionamide, isoniazid and cycloserine	15	15
Ethambutol, ethionamide, isoniazid, cycloserine and kanamycin	21	15
Ethambutol, ethionamide, isoniazid and kanamycin	43	36
Ethambutol, ethionamide, isoniazid, viomycin and cycloserine	9	8
Ethambutol, isoniazid and kanamycin	1	0
Ethambutol and isoniazid	2	1
Total	107	90

treatment were analyzed. Analysis of the effects of race, sex, age, toxicity, degree of tuberculosis, months of previous hospitalization, the last drug treatment group, months on that treatment, and the last sputum and specific antimycobacterial titers obtained, results obtained by x-ray examination and overall treatment results were also made.

RESULTS OF ANALYSIS

There were so many variables and so many unassessable points that it was difficult to make any valuable statistical interpretation.

There is not sufficient evidence at the 5 per cent probability level to indicate a correlation between the sputum results and sex, antimycobacterial titer, or months of previous hospitalization.

The correlations between sputum results and race and age are significant at the 5 per cent probability level. By the fourth month, about 70 per cent of the patients had converted. The rate of conversion de-

creases with time. Sputum conversion occurs earlier in colored than in white patients. Sputum conversion occurs earlier in younger aged than in older aged patients.

The effects of drug treatments are confounded with the duration of the time on the drug and the duration of time in the study. However, it appears that negative sputums are acquired earlier with the addition of kanamycin to the primary drug regimen of ethambutol, ethionamide and isoniazid. It also appears that negative sputums occur earlier when cycloserine or viomycin are added than with the original three drug treatments (ethambutol, ethionamide and isoniazid).

The correlation between x-ray findings and overall treatment results with the sputum findings is significant at the 1 per cent probability level.

CURRENT STATUS

Sixteen (15 per cent) of the patients are dead. This is a reflection of the relatively hopeless situation many were in at the beginning of the study. Ten of the deaths occurred during hospitalization; five of these were due to progressive tuberculosis; two were nontuberculous deaths; one died of a brain tumor; one died following surgery,

TABLE 7—RESULTS
SPUTUM CONVERSION OBTAINED IN 90
(84 PER CENT) OF THE 107 PATIENTS

Conversion During	Number
1st month	26
2nd month	18
3rd month	13
4th month	16
5th month	4
6th month	5
7th month	4
8th month	0
Converted after 8th month	3
Still positive	17
Converted with surgery	1
Total	107

TABLE 8—TOXICITY

	EMB	ETH	KM	Total	Per Cent
No toxicity	80			80	(75%)
Toxicity	27			27	(25%)
Total				107	
Temporary drug interruption	6*	9*	6	19	18
Permanent drug interruption	4	0	4	8	7

*One patient was intolerant at some time, to some degree to two drugs employed.

and one was a suicide. Six died after receiving medical discharge—none from progressive tuberculosis.

A minimum of six consecutive months of negative sputum cultures was necessary for a patient to qualify for medical discharge.

Ninety (84 per cent) patients have had reversal of infectiousness. Ten are still hospitalized and negative. One still hospitalized was negative for five months and then became positive again.

Seventy-four were given medical discharges to continue on drugs to which they were resistant, for the most part. The average duration of post hospital observation is 11 months. Each patient has averaged two sputum specimens per month submitted for culture after discharge. They have all had routine x-ray observations. Five discharged, plus one during hospitalization have reactivated to date—a bacteriologic relapse rate of 6.6 per cent.

CONCLUSIONS

(1) Ninety (84 per cent) of the 107 patients with drug resistant infection obtained reversal of infectiousness.

(2) Seventy per cent of the reversal of infectiousness occurred by the fourth month.

(3) Sputum conversion occurred earlier in colored than in white patients.

(4) Sputum conversion occurred earlier in younger aged than in older aged patients.

(5) The high death rate, 15 per cent, was attributable mostly to the ravages of the pre-existing disease.

(6) There was no true toxicity to ethambutol. Not one patient exhibited more than temporary blurring of the vision. This subjective manifestation was not substantiated by visual acuity testing nor eyeground observation in any instance.

(7) There was no significant correlation between sputum conversion and specific antimycobacterial titers.

(8) The bacteriologic relapse rate to date is 6.6 per cent.

CONCLUSIONES

(1) Noventa (84 por ciento) de los 107 casos con resistencia a las drogas fueron convertidos en no infectantes.

(2) En el setenta por ciento esta conversión ocurrió hacia el cuarto mes.

(3) La conversión de la expectoración se observó más tempranamente entre los sujetos de color que entre los blancos.

(4) La conversión de la expectoración tuvo lugar antes en los sujetos jóvenes que entre los de edad más avanzada.

(5) La alta mortalidad, 15 por ciento, puede ser atribuida a los estragos de la enfermedad preexistente.

(6) No se observó verdadera toxicidad con el etambutol, ni otras manifestaciones tóxicas que ana disminución temporal de la agudeza visual. Este trastorno subjetivo no pudo ser corroborado en caso alguno por las pruebas visuales o la fundoscopia.

(7) No se comprobó correlación alguna de significación entre la proporción de conversiones del esputo y los resultados de las titulaciones de la potencia antimicobacteriana.

(8) La proporción de relapsos bacteriológicos hasta la fecha es de un 6.6 por ciento.

RESUMÉ

(1) 90 malades (84%) sur 107 dont les germes étaient résistants aux médicaments antibactériens ont obtenu la récession de leur infection.

(2) Dans soixante dix pour cent des cas cette récession de l'infection survint après le quatrième mois.

(3) La négatification de l'expectoration survint plus tôt chez les malades de couleur que chez ceux de race blanche.

(4) La négatification de l'expectoration survint plus tôt chez les malades jeunes que chez les malades âgés.

(5) Le taux de mortalité élevé, 15%, fut imputable pour la plus grande part aux troubles dus à l'état antérieur.

(6) Il n'y eut pas de véritable toxicité due à l'éthambutol. Aucun malade n'eut d'autres troubles qu'un obscurcissement temporaire de la vision. Cette manifestation subjective ne fut concrétisée dans aucun cas ni par le contrôle de l'acuité visuelle, ni par l'examen du fond d'oeil.

(7) Il n'y eut aucun rapport significatif entre la négatification de l'expectoration et le titrage antimicrobien spécifique.

(8) Le taux de rechute bactériologique à ce jour est de 6,6%.

ZUSAMMENFASSUNG

(1) 90 (84%) der 107 Medikamenten-resistenten Patienten wurden rückfällig infektiös.

(2) 70% der rückfälligen Infektiosität trat im 4. Monat auf.

(3) Die Konversion des Sputums zeigte sich bei Negern früher als bei Weißen.

(4) Die Sputumkonversion fand sich früher bei jüngeren als bei älteren Patienten.

(5) Die hohe Sterblichkeitsziffer, 15%, war meistens den verheerenden Auswirkungen der früheren Erkrankung zuzuschreiben.

(6) Es fand sich keine echte Toxizität von Ethambutol. Kein Patient wies mehr als vorübergehend ein verschwommenes Sehen auf. In keinem Fall war diese subjektive Erscheinung objektiviert worden durch Sehschärfepfung oder Augenspiegelung.

(7) Es bestand keine signifikante Korrelation zwischen der Sputumkonversion und spezifischen Antimykobakterien-Titern.

(8) Die bakteriologische Rezidivrate beträgt zur Zeit 6,6%.

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For reprints, please write: Dr. Corpe, Battey Hospital, Rome, Georgia.

CONGENITAL PARTIAL RIGHT PERICARDIAL DEFECT

A case of congenital partial right pericardial defect associated with herniation of the right atrial appendage is reported. The radiologic studies in this anomaly revealed certain characteristics. The routine chest roentgenogram disclosed an abnormal cardiac configuration with a smooth localized protuberance on the right cardiac border. On fluoroscopic examination, this projection showed active pulsations ap-

parently paradoxical to those of the right ventricle. Angiocardiographic examination showed herniation of the right atrial appendage through the partial pericardial defect, confirming the diagnosis.

CHANG, C. H. AND AMORY, H. I.: "Congenital Partial Right Pericardial Defect Associated with Herniation of the Right Atrial Appendage," *Radiology*, 84:660, 1965.

ELECTROCARDIOGRAPHIC FINDINGS DURING CORONARY ANGIOCARDIOGRAPHY IN MAN

Electrocardiogram modifications were studied during coronary angiography in 38 coronary patients under general and local anesthesia. During introduction of the radiopaque fluid into the aorta, in relation to the preliminary electrocardiogram, a slight increase in heart rate was observed, and an increase in the amplitude of the P wave, without any significant variations in its duration and A-V conduction time. The ventriculogram in a majority of cases showed a reduction in the amplitude of the QRS waves without any modifications in ventricular conduction time.

The S-T segment showed in general slight depression, while the T-Wave on the average underwent only small modifications with the exception of two cases in which an injury current was observed which rapidly disappeared after removal of the catheter. In one case, premature ventricular beats, immediately after introduction of the radiopaque fluid, were seen and disappeared in a short time.

TRONCONI, L., MONTEMARTINI, C. AND BALDRIGHI, V.: "Electrocardiographic Findings During Coronary Angiocardiography in Man," *Cor et Vasa*, 7:18, 1965.

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