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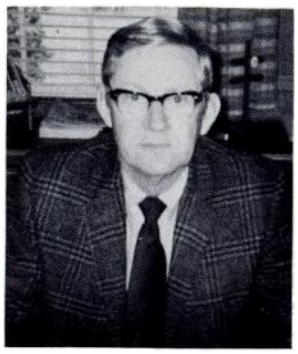

Dr. Corpe

By the time rifampin became available in the United States for experimental clinical trials, highly effective drug regimens were already available and well established for the treatment of tuberculosis.[1-14]

Battey State Hospital had the opportunity to participate with 19 other hospitals in a United States Public Health Service Cooperative Therapy Trial studying rifampin in the initial treatment of pulmonary tuberculosis. It was our hope that the information contributed from this hospital might be used to help secure Food and Drug Administration approval for the general use of the drug in the United States for the treatment of tuberculosis. This report will deal with 192 patients from Battey State Hospital, admitted to this study starting in July, 1969 and ending in May, 1970.

Materials and Methods

The selections were predetermined by the protocol. We admitted men patients, positive to direct smear, with far or moderately advanced pulmonary tuberculosis. Each patient was expected to remain in the hospital for a 20-week period and was *not* excluded by any of the following:

1. Under 14 years.
2. Previous treatment for more than two weeks with streptomycin, isoniazid, ethambutol or rifampin.
3. Renal disease of sufficient degree to result in impaired excretion of the antituberculosis chemotherapeutic agents or where aggravation of existing renal condition might ensue from their administration.
4. Significant hepatic dysfunction.
5. Previous history of white blood cell count below 4,500.
6. Various ophthalmic conditions which might make changes in visual acuity difficult to evaluate.
7. Any other pre-existing condition which, in the opinion of the investigator, introduces undue risk in the presence of streptomycin, isoniazid, ethambutol or rifampin.

At a later date a few women were admitted if assurance could be made that they would not become pregnant during the 20-week period.

The following *laboratory determinations* were completed on all patients admitted to the trial prior to starting treatment.

Urinalysis: Specific gravity; albumin, glucose; sediment
Chemistry: BUN; uric acid; fasting blood surgar, SGPT; alkaline phosphatase; bilirubin
Hematology: Hematocrit, hemoglobin; WBC; differential; platelet count

*From the Battey State Hospital, Rome, Georgia.

Not only were these patients seen daily by a physician for observation of any untoward signs or symptoms, all the above tests were repeated at least every two weeks during the study.

All patients had five sputum specimens submitted to our laboratory on admission. Sensitivity studies were done for the four drugs to be used in the study, plus several others, on every positive culture obtained from any patient during the entire study and observation period. Sputum studies were done at least one time every two weeks.

A roentgenogram was taken every four weeks and was compared to the admission x-ray film by the authors. The presence of cavitation at the beginning of the study was determined not only by a PA film, but also by planigrams. No cavity was said to be closed without planigraphic confirmation. X-ray films were read every four weeks and coded to show either no change, slight improvement, moderate improvement, or marked improvement.

Treatment Regimens

Every patient in this study was started on triple drug therapy of daily streptomycin, isoniazid and PAS on the day of admission to the hospital. As soon as it had been established that each patient met the criteria for entrance into the study, the central research office of the United States Public Health Service in Bethesda was notified. The moderate and far advanced cases were separately randomized there between the following regimens. These patients received approximately one week of triple drug therapy prior to regimen assignment.

Regimen No.

1. Rifampin—isoniazid
2. Rifampin—isoniazid—ethambutol
3. Streptomycin—isoniazid—ethambutol
   NOTE: SM daily 1-8 weeks
   twice weekly 9-20 weeks

Dosage

The entire dosage of each drug used in the study was given in a single daily dose in the following amounts:

Drug	Dose	Tablet size
Rifampin	600 mg daily	300 mg
Isoniazid	300 mg daily	100 mg
Streptomycin	1 gm daily or twice weekly	(Injectable)
Ethambutol	15 mg/kg daily	400 mg

Table 1—*Race and Sex Distribution*

Negro Men	111
White Men	60
Negro Women	14
White Women	7
	192

The doses of ethambutol and streptomycin were approximately according to the following schedule:

Weight at beginning of study	Dose of ethambutol	Dose of streptomycin
Less than 100 lb	600 mg	½ gm
100-119 lb	800 mg	¾ gm
120-139 lb	800 mg	1 gm
140-159 lb	1,000 mg	1 gm
160 lb or more	1,200 mg	1 gm

The dose of streptomycin was reduced to ½ gram for patients over 65 years of age.

Dosages were not adjusted with changes in body weight during the trial except when extreme weight losses occurred.

Rifampin, ethambutol and isoniazid were given in single daily doses in the morning; rifampin was given at least one-half hour before breakfast.

Nearly two-thirds of the patients admitted to the study were Negroes and nearly 90 percent were men (Table 1). Each patient was assigned randomly to a regimen by the central office (Table 2). Twenty-five patients were eliminated for the reasons shown in Table 3, leaving 169 for final analysis.

The age of patients admitted to final analysis is summarized in Table 4. The ages of the patients assigned to the three regimens were similar to a 95 percent confidence level (X^2 contingency table). The bacteriologic status of the patients assigned to the three regimens were similar with a 100 percent confidence level as all were positive by both direct smear and culture on admission to the study (Table 5). Thirty patients had moderately advanced tuberculosis and 139 had far advanced tuberculosis (Table 6). The distribution between the three regimens by extent of disease was similar, with a X^2 confidence level above 95 percent. Thirty-nine patients had single cavities, 56 had multiple unilateral cavities, 58 had multiple bilateral cavities, and 16 were noncavitary (Table 7). The distribution by the extent of cavitation was similar between the three regimens with a X^2 confidence level above 95 percent.

Table 2—*Regimens Assigned to 192 Patients*

Regimen	Daily dose	No. patients
1. Rifampin + Isoniazid	600 mg + 300 mg	65
2. Rifampin + Isoniazid + Ethambutol	600 mg + 300 mg + 15 mg/kg	65
3. Streptomycin + Isoniazid + Ethambutol	1 gm* + 300 mg + 15 mg/kg	62

*Daily 1-8 weeks and biweekly 9-20 weeks.

Table 3—*Reasons for Patient Elimination*

	Reg 1 (R + I)	Reg 2 (R + I + EMB)	Reg 3 (SM + I + EMB)	Total
No. admitted to trial	64	65	63	192
No. not fulfilling admission criteria				10
(A) Atypical tubercle bacilli	2	4	2	
(B) Pre-existing kidney disease			2	
No. excluded from final analysis				13
(A) Premature self dischg	4	1	4	
(B) Toxicity		1	2	
(C) Refused SM injections			1	
No. used for final analysis	58	59	52	169

Results

Whether or not a patient can tolerate an assigned drug regimen is of paramount importance (Table 8). Isoniazid was well accepted by patients and not one of the 169 had any intolerance to the drug. Of the 117 patients receiving rifampin, one patient developed leg cramps, reduplicated on rechallenge, necessitating discontinuance of the drug (0.09 percent). One hundred eleven patients received ethambutol and one patient had an allergic reaction characterized by a dermatitis (0.09 percent). Two of the 52 patients receiving streptomycin had allergic reactions necessitating a regimen change (3.9 percent). We compared each regimen to 100 percent. One hundred percent of the patients took rifampin and INH without any untoward reaction; 99 percent of those taking rifampin, INH and EMB and 96 percent of those taking SM, INH and EMB were able to do so without any untoward reaction.

Table 4—*Initial Clinical Data on Patients Admitted to Final Analysis*

	R + I	R + I + EMB	SM + I + EMB
No. Patients	58	59	52
Characteristics			
Age, years			
Average	46.5	47.8	45.4
Median	46	48	45
Range	22-81	20-81	18-81

Table 5—*Initial Clinical Data on Patients Admitted to Final Analysis*

	R + I	R + I + EMB	SM + I + EMB	Total
No. Patients	58	59	52	169
Characteristic				
Bacteriology on adm				
(+) By direct smear and culture	58	59	52	

Table 6—*Initial Clinical Data on Patients Admitted to Final Analysis*

	R + I	R + I + EMB	SM + I + EMB	Total
No. Patients	58	59	52	169
Characteristic				
Extent of disease				
Moderate	11	12	7	30
Far advanced	47	47	45	139

Table 7—*Initial Clinical Data on Patients Admitted to Final Analysis*

	R + I	R + I + EMB	SM + I + EMB	Total
No. Patients	58	59	52	169
Characteristic				
Extent of cavitation				
Single	13	16	10	39
Multiple unilateral	20	23	13	56
Multiple bilateral	19	14	25	58
No cavity	6	6	4	16
	58	59	52	169

Table 8—*Drug Allergy or Toxicity Requiring Drug Discontinuance*

	R + I	R + I + EMB	SM + I + EMB
No. patients at risk	58	59	52
No. requiring discontinuance	0	1*	2**

*Responsible drug—Rifampin
**Responsible drug—Streptomycin (1)
Responsible drugs—Double Allergy to SM and EMB

Table 9—*X-Ray Film Clearance At end of 5th Month*

	R + I		R + I + EMB		SM + I + EMB	
	(No)	(%)	(No)	(%)	(No)	(%)
No. Change	1	2	1	2	0	
Minimal	9	16	8	13	6	12
Moderate	19	33	22	37	15	29
Extensive	27	46	29	48	29	56
Worse	1	2	0		2	4

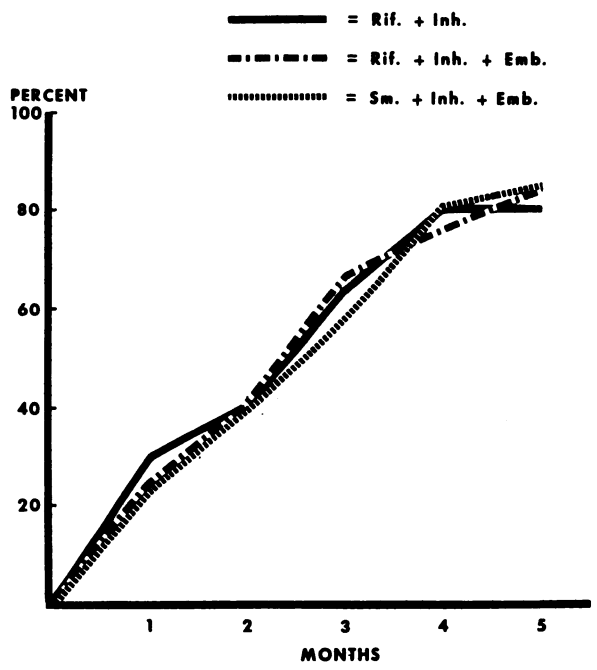

FIGURE 1

Two of the 192 patients entering the study died, both from respiratory insufficiency and heart failure. One patient had positive sputum at the time of death.

The improvement on x-ray examination, as evidenced by the three regimens, is shown in several ways. The proportion of patients with minimal, moderate and extensive clearance and those with no change or worsening were similar on all regimens (Table 9). This similarity is demonstrated graphically (Fig 1) by combining those with moderate and extensive clearance. Approximately 80 percent of the patients on either of the regimens revealed moderate or extensive clearance. The absence of cavitation was determined by planigrams at the beginning and end of the study. The percentages of patients who closed their cavities under the various regimens are as follows: 32 percent for rifampin + isoniazid; 36 percent for rifampin + isoniazid + ethambutol; 38 percent for streptomycin, isoniazid and ethambutol. There was no significant regimen superiority for cavity closure.

Sputum Conversion

The date of sputum conversion was retrospectively set when the first negative smear and culture was procured and was never followed by either a positive smear and/or culture. The length of time required to secure sputum conversion is of practical importance. It relates to the length of hospitalization and the communicability or infectiousness of the disease.

On rifampin + isoniazid the percentages of patients converted by month are as follows: month 1—24 percent; month 2—34 percent; month 3—67 percent; month 4—78

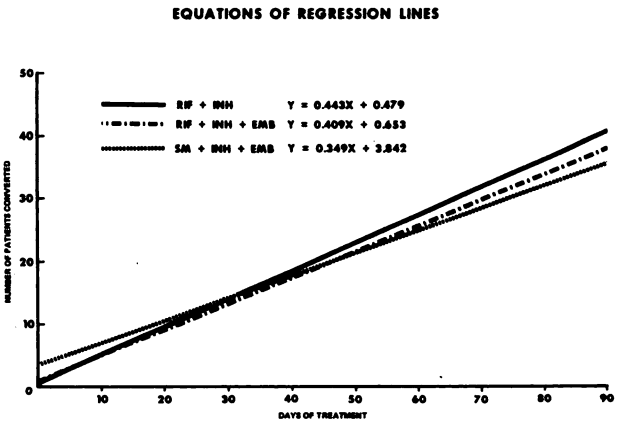

FIGURE 2

percent; month 5—88 percent.

On rifampin, isoniazid and ethambutol the conversion rates by month are as follows: month 1—20 percent; month 2—34 percent; month 3—63 percent; month 4—81 percent; month 5—90 percent.

On streptomycin + isoniazid + ethambutol the comparable conversion rates are: month 1—10 percent; month 2—31 percent; month 3—54 percent; month 4—71 percent; month 5—94 percent.

From the above data it can be seen that a fairly definite relation exists between the length of time in which conversion was achieved and the number of patients converted. The regression equations give one representation of this relationship. The equations generalize the pattern of conversion and allow one to predict the number of people that can be converted at any given number of days of treatment.

The regression equations (Fig 2) demonstrate the line for regimen 1 had a greater slope than either of the other two. This would imply that there is a higher conversion rate for rifampin + isonialid in the long run. The homogeneity of the regression coefficient was tested using the F statistics. The results were significant at the 99 percent confidence level, implying that there was indeed a significant difference in the regimens. Thus regimen 1 stands above the other regimens in terms of conversion.

There was no development of resistant organisms.

Surgery

Three patients on regimen 3 (SM + INH + EMB) had surgery. The results previously shown were influenced only in regard to cavitary status, where one cavity was removed during the 20-week treatment. One patient had surgery after the 20-week treatment period and the third patient had the insertion of intrapleural catheters for bilateral spontaneous pneumothoraces.

SUMMARY

Rifampin combined with isoniazid resulted in a regimen with very little toxicity (1 percent). Both drugs were administered orally, with excellent patient acceptance. The sputum conversion analysis deemed it to be the superior regimen. This regimen did as well as either of the other two in bringing about favorable changes on x-ray films.

The main obstacle to widespread utilization of the drug is cost.

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