VARIATIONS IN TUBERCULIN SENSITIVITY IN TUBERCULOUS CHILDREN AFTER TREATMENT

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Before the use of antituberculosis drugs, variations in the tuberculin sensitivity of tuberculosis patients were frequently noticed and reported in medical literature.[1, 2, 3] The studies continued in this field after the use of antituberculosis drugs. We find in our study of the literature of the field that various reports have been made, many contradictory, on the matter of change in sensitivity in Mantoux tests, after treatment with various drugs. Feldman, Hinshaw and Mann [4] and Steenken and Wolinsky [5] reported the decrease of tuberculin sensitivity in animals after Streptomycin treatment. In a subsequent study Steenken and Wolinsky made the same observation after INH (isonicotinyl - hydrazine) treatment.[6] Barnwell, Burn and Walker[7] observed that Streptomycin therapy had no effect on humans, but Woodruff, et al[8] noted an increase in tuberculin sensitivity in the critically ill patient. Criep and Levine [9] after one month INH treatment observed no inhibition of tuberculosis reaction. However, the Veterans Administration report [10] noted a decrease in tuberculin sensitivity in adults after INH treatment. Hewell and Suyemoto[11] reported that in a study of 483 adult patients, of whom 352 were treated with INH alone, some cases showed no change, some cases showed an increase and some cases showed a decrease in tuberculin sensitivity.

One of the more remarkable reports was made by Robinson, Meyer and Middlebrook[12] on 13 children treated with INH alone. Six children, all under two, had essentially negative chest roentgenograms, but positive Mantoux reactions on admission. Four of these six children, after six to seven months treatment, developed negative tuberculin reactions, and only two remained the same. The other seven patients had positive Mantoux reactions and positive roentgenograms of the chest on admission, and were still reacting positively after treatment.

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We tried in our study to observe the results in a larger child population than had previously been tested using several different therapeutic agents.

We also observed the treatment and made periodic tests over a longer time span than had previously been attempted. One of the aims of our study was to note the relation between roentgen ray findings in the course of treatment. Another was to relate the tuberculosis involvement of organs other than the chest.

Material and Methods

This study was made of 131 tuberculous children between four months and 13 years of age from the pediatric division of Seaview Hospital. Thirty - three patients were being treated with several therapeutic agents, 98 patients with INH alone, 8 mg. per kg. The duration of treatment was between four months and 30 months. All of the patients received 1/10,000 dilution Mantoux tests on admission to the hospital. The solution we used was prepared by the Department of Health, New York City, from old tuberculin, and throughout our investigation we used fresh, controlled samples of this preparation. The tests on all patients were made by us on the flexor surface of the forearm with intracutaneous injection, and were read by us 72 hours later. All patients who had a negative reaction using a 1/10,000 dilution were retested with a 1/1000 dilution. Again all patients who had negative reactions using a 1/1000 dilution were tested with a 1/100 dilution. The results of all were read at the prescribed intervals.

Results

Patients Treated with INH Alone

Of the 98 patients treated with only INH, 40 were treated for a period of from four to six months. Thirty - nine of the patients, tested with the old tuberculin 1/10,000 dilution, reacted positively on admission. The remaining patient reacted positively when tested with a 1/1000 dilution.

After treatment, 12 patients showed no change; 18 patients were still positive when given the 1/10,000 dilution but their reactions were not as marked. Of the remaining ten patients who were negative with the 1/10,000 dilution, six were still negative when tested with the 1/1000 dilution, and only one remained negative with the 1/100 dilution.

There were 43 patients treated with INH alone for six to 12 months. Twenty of these patients showed no change after treatment; 14 were still positive with the 1/10,000 dilution, but showed a slight decrease in reaction, and nine reacted negatively. Only six children remained negative when tested with a 1/1000 dilution. All of the patients reacted positively when the 1/100 dilution was used.

Seven patients were treated with INH for a period of 12 to 18 months. Five showed no change; two were positive but again showed a decrease in reaction to the 1/10,000 dilution.

Four patients were treated for 18 to 24 months. Two showed a decreased positive reaction when tested with a 1/10,000 dilution. Two of them reacted negatively with 1/10,000 dilution but when tested with the 1/1000 dilution were positive.

Finally four patients were treated for more than 24 months. Three of these children showed no change, one child was negative with the 1/1000 dilution, but positive when the 1/100 dilution was used (table 1).

TABLE 1

CASES TREATED WITH INH

BEFORE TREATMENT			AFTER TREATMENT				
Duration of Treatment	1/10,000 Positive	1/1000 Positive	Decrease of Reaction to 1/10,000	1/10,000 Negative	1/1000 Negative	1/100 Negative	No Change
Less than 6 Months	39	1	18	4	5	1	12
6 — 12 Months	42	1	14	3	6	—	20
12 — 18 Months	7	—	2	—	—	—	5
18 — 24 Months	4	—	2	2	—	—	—
Over 24 Months	3	1	—	—	1	—	3
TOTALS	95	3	36	9	12	1	40

Patients Treated with more than one Agent

Thirty - three patients were treated with more than one agent. Ten were treated with a combination of INH and PAS (para - aminosalicylic acid). Nine reacted positively with the 1/10,000 dilution upon admission and one with the 1/1000 dilution. During the control test, five of them showed no change, two were still positive,

but showed a decreased reaction, and three were negative until tested with the 1/100 dilution.

Two patients were treated with INH and Streptomycin. One showed no change and the other was negative until tested with the 1/1000 dilution.

Twenty-one patients were treated with triple drugs. Thirteen patients showed no change, four patients remained positive, but showed a decreased reaction, and three were negative when tested with a 1/10,000 dilution. However, only one remained negative when tested with a 1/100 dilution (table 2).

TABLE 2

CASES TREATED WITH MORE THAN ONE AGENT

BEFORE TREATMENT			AFTER TREATMENT				
Type of Treatment	1/10,000 Positive	1/1000 Positive	Decrease of Reaction to 1/10,000	1/10,000 Negative	1/1000 Negative	1/100 Negative	No Change
INH - PAS	9	1	2	—	3	—	5
INH - STREP	2	—	—	1	—	—	1
Triple	21	—	5	1	1	1	13
TOTALS	32	1	7	2	4	1	19

Negative Reactions (according to age and organ involvement)

Twenty-two patients who were treated with INH alone over varying periods of time tested negative to a 1/10,000 dilution. Of the nine children who (as shown in table 1) were negative until tested with the 1/1000 dilution, four were in the two to five year age group, and five were between five and ten years of age. Of these nine children, one was associated with pleural effusion, and one with peritonitis tuberculosis (see table 3). According to the children's roentgenograms on admission, two of then were essentially negative, one showed atelectasis, and six showed slightly prominent and enlarged lymph-nodes. After treatment, seven children had essentially negative roentgenograms, one showed clearing and one showed no change.

Of the 12 patients who were negative until tested with the 1/100 dilution, one child was less than two years old, three were between two and five years, and eight were in the six to ten age

TABLE 3
NEGATIVE CASES AFTER TREATMENT

Treated with INH		AGES				Association with the other Organs				Chest Roentgen ray Findings before Treatment			Chest Roentgen ray Findings after Treatment		
Number of Cases	Ratio of Mantoux	2	2—5	5-10	10 +	Meninges	Pleura	Periton	Bone	Essentially Negative	Large İnfiltration or Atelectasis	Slightly Prominent or Enlarged Lymph Nodes	No Change	Clearing	Essentially Negative
9	1/10,000	—	4	5	—	—	1	1	—	2	1	6	1	1	7
12	1/1,000	1	3	8	—	2	—	1	—	5	1	6	1	3	8
1	1/100	1	—	—	—	—	1	—	—	—	—	—	—	—	—
Treated with more than one Agent															
2	1/10,000	—	1	1	—	1	—	—	—	—	—	2	—	1	1
4	1/1,000	—	1	2	1	—	—	—	1	—	3	1	—	4	—
1	1/100	—	1	—	—	—	—	—	—	—	1	—	—	1	—

group. Two of their cases were associated with meningitis tuberculosis, and one with peritonitis. Five of the the roentgenograms were considered essentially negative on admission, one showed large atelectasis, and six revealed slightly prominent and enlarged hilus lymph nodes. During the course of our study, eight of the children showed essentially negative. Three showed some clearing, and one no change.

One child under two, whose roentgenogram showed pleural effusion on admission, remained negative during the course of the tests even with the 1/100 dilution and his roentgenograms were essentially negative.

Seven patients who were treated with more than one agent tested negatively at different levels. Two of them, one in the two to five, one in the five to ten age groups, were negative until tested with the 1/1000 dilution. One of them was associated with meningitis. Both of their roentgenograms taken on admission showed slightly prominent or enlarged hilar lymph nodes. After treatment, one roentgenogram was essentially negative, the other showed some clearing.

Of the four children between two and 13, who were negative until tested with a 1/100 solution, only one had another involvement (bone). On admission, three of them had large infiltration or atelectasis, one had a slightly prominent hilar shadow. After treatment, all four showed some clearing on roentgen ray examination.

One child, whose roentgenogram showed atelectasis on admission, continued to react negatively when tested with a 1/100 dilution after treatment. His roentgenogram revealed some clearing.

Discussion

Of the 98 children who were treated with INH alone, 40 showed no change after treatment. Thirty-six continued to react positively, but showed a decreased reaction, and 22 reactions remained negative using a 1/10,000 dilution. Of these 22, only one remained negative with a 1/100 dilution. This demonstrates that after treatment approximately 40 per cent of the patients showed no change and 60 per cent showed a decrease in their tuberculin sensitivity to different degrees.

Of the 33 children who were given the combined treatment, 19 (58 per cent) showed no change after treatment, seven were still positive, but showed a decreased reaction, and seven were negative on different sensitivity levels. Only one remained negative with a

1/100 solution. Forty-two per cent showed a decreased reaction to different degrees.

Our observations indicated that there was no remarkable difference between the INH and combined treatments as far as tuberculin hypersensitivity is concerned. However, we found the decrease in reaction on different levels (only 1.6 per cent became negative) less remarkable than Robinson's[12] observations.

A question that could be profitably studied in further research is what should be done with the children who have lost their tuberculin sensitivity.

Summary

This study was made of 131 children between four months and 13 years of age, all of whom were treated for periods of time ranging from four months to two and a half years. During this period we used INH alone on a group of 98 children and more than one agent (INH - PAS, INH - Strep., and INH - PAS - Strep.) on 33 patients. We observed that 60 per cent of our patients showed a decrease in tuberculin reaction after INH treatment and that 42 per cent of those who received the combined treatment showed a decreased reaction. Only two children became negative at the end of the test.

REFERENCES

1. Schwartz, W. S., and Heise, F. H.: Variations in tuberculin sensitiveness in tuberculosis patients, Am. Rev. Tuberc. **24**: 479, 1931.

2. Hayes, M. G., Pastor, J. R., Gaston, L. R., Gory, R. A. S., and Long, E. R.: Tuberculin skin sensivity in chronic tuberculosis in the course of hospital treatment, Am. J. of Sc. **194**: 220, 1937.

3. Appel, J. M., Douglas, B. H., Jocz, T. R., and Willis, H. S.: Relation between tuberculin allergy and clinical course, Am. Rev. Tuberc. **36**: 303, 1937.

4. Feldman, W. H., Hinshaw, H. C., and Mann, F. C.: Streptomycin in experimental tuberculosis, Am. Rev. Tuberc. **52**: 269, 1945.

5. Steenken, W. Jr., and Wolinsky, E.: Streptomycin in experimental tuberculosis; its effect upon well - established progressive tuberculous infection in guinea pigs, Am. Rev. Tuberc. **56**: 227, 1947.

6. Steenken, W. Jr., and Wolinsky, E.: Antituberculosus properties of hydrazines of isonicotinic acid. (Rimifon Marsilid), Am. Rev. Tuberc. **65**: 365, 1952.

7. Barnwell, J. B., Burn, P. A., and Walker, A. M.: The effect of Streptomycin upon pulmonary tuberculosis. Preliminary report of a cooperative study of 223 patients by the Army, Navy and Veterans Administration, Am. Rev. Tuberc. **56**: 485, 1947.

8. Woodruff, C. E., Steininger, W. J., Kelly, R. G., and Kreisel, H.: Response to antimicrobial therapy of anergic and partially anergic tuberculous patients; changes in tuberculin sensitivity of individual patients, Am. Rev. Tuberc. **67**: 286, 1953.

9. Criep, L. H., and Levine, M. E., Effect of Isoniazid on tuberculin test, Am. Rev. Tuberc. **67**: 535, 1953.

10. Army and Navy study on the chemotherapy of tuberculosis, Quarterly report of the Veterans Administration, June 29, 1952.

11. Hewell, B., and Suyemoto, D.: Tuberculin reactions of tuberculous patients on isoniazid therapy: preliminary report, Am. Rev. Tuberc. **69**: 733, 1954.

12. Robinson, A., Meyer, M., and Middlebrook, G.: Tuberculin hypersensitivity in tuberculous infants treated with isoniazid, New England J. Med. **252**: 983, 1955.

13. Editorial, Reversal of tuberculin reactivity, New England J. Med. **253**: 388, 1955.