Reversal of Tuberculin Reaction
in Early Tuberculosis

JOHN M. ADAMS, M.D., F.C.C.P., VAUGHAN A. KALAJAN, M.P.H.,
BYRON O. MORK, M.D., MAXWELL ROSENBLATT, M.D., F.C.C.P.,
W. J. ROTHROCK, M.D. and BERNARD J. O’LOUGHLIN, M.D., F.C.C.P.
Los Angeles, California

Introduction

The traditional concept that the tuberculin reaction when positive will remain so for the rest of the patient’s life has been widely accepted for many years. The present study was carried out to detect tuberculosis in its earliest phases by means of a positive tuberculin reaction in individuals who reacted negatively to previous test or tests. These positive patients were then followed by repeated tuberculin tests for signs of change in their reactions. The opportunity to study the natural history of tuberculosis has been provided in the tuberculosis clinics of the Los Angeles Health Departments where hundreds of tests performed weekly on contacts made it possible to select individuals whose skin reactivity changed from a negative test to a positive one.

In the past two years 160 individuals have been discovered with a known negative test who have converted to a positive reaction within three months or within 12 months or were infants under one year of age who were found to have a positive reaction. It has been assumed in the case of infants under one year that they were early converters. One hundred twenty one individuals have been tested two or more times and 68 of these have changed from a positive reaction to a negative one. A total of 618 tests have been done on the entire group of 160 subjects. Although all of the subjects in order to be accepted in the study had an initial negative test or were under one year of age, the high rate of change from a positive to a negative test was very surprising.

A search of the literature has revealed a few papers in which the instability or reversibility of the tuberculin reaction has been found. Dahlstrom¹ pointed to the finding of “calcified nodules, presumably of tuberculous origin” in individuals not reacting to tuberculin and raised the question as to whether or not this might indicate a loss of tuberculin allergy after complete healing. He showed a clear relation between the intensity of allergy and the probability of its ultimate disappearance. His data revealed that over 70 per cent of those showing the “weakest detectable reaction” (one plus) lost their allergy, and that 62 per cent of those individuals with a two plus reaction subsequently became negative. With respect to age factors, he further points out that reversibility occurs in early life in an overwhelming majority and is rare in adult life.

Blatman, Rapmund, Newstrand, and Alexander² also state that “changes in tuberculin allergy have been surprising,” and they found no difference in the patients with positive as opposed to negative gastric contents in

¹ From the Departments of Pediatrics, Preventive Medicine and Public Health, and Radiology, School of Medicine, University of California.
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regard to the degree of reduction of allergy to tuberculin. When they tested their 106 subjects, all under three years of age, 40 per cent were found to be negative at 12 months to the same dose of PPD or OT which was used initially. At 18 months, 54 per cent were negative, and when the negative subjects were retested with 1.0 milligram of OT, the overall percentage of negative skin tests became 40 per cent.

Galien and Hamman\(^3\) reported in 1913 on patients who received repeat tuberculin tests and they showed a reversal to negative in 50 per cent of those retested. A recent report by Robinson, Meyer and Middlebrook\(^4\) in 1955 indicated a reversal in skin allergy in a few patients treated with isoniazid (INH). In no instance have we found a study on reversal of tuberculin allergy in which the subjects were studied prior to the development of a positive skin reaction. A study of nurses by Tukey, et al.\(^5\) revealed a lack of sensitization following repeated skin tests in subjects who had no allergy to tuberculin. However, they stated that “fluctuation was also expressed by frequent reversions to negative reaction.” Aronson\(^6\) reported on fluctuations in the tuberculin reaction among the BCG vaccinated Indian tribes which he studied and found the reversion rates to be highest at the Pima Agency, Arizona. Among the unvaccinated controls the fluctuation was higher than in other areas and “reversions from positive to 0.005 mg. of PPD to negative or doubtful were conspicuously high.” It is of interest that a study of 80 individuals with disappearance of “skin hypersensitivity” was carried out by Paretzky\(^7\) in the clinics of the Los Angeles County Health Department over 20 years ago. When retesting was done with a large dose (10 mg. of tuberculin) it was found that two-thirds of the subjects remained negative. The author concluded, “Immunity is considered as the causative factor of the disappearance of the specific skin hypersensitiveness.”

**Methods and Materials**

*Case Findings:*

This study was carried out with the cooperation of the County and City of Los Angeles Health Departments and except for a few patients who were followed at the University of California Medical Center, and in sanatoriums, all subjects were registered either in the city or county tuberculosis clinics.

The selection of subjects was based on a known negative tuberculin test within a three month interval (Group B) or within a 12 month interval (Group C) prior to the finding of a positive reaction, except for infants (Group A) who were assumed to have had a previous negative test when the positive test was found under one year of age.

*Tuberculin Testing:*

The test material was purified protein derivative (PPD) administered intradermally on the ventral surface of the mid-forearm, and the doses employed were 5 units (.0001 mg.) of tuberculin in the city clinics and 25 units (.0005 mg.) of tuberculin in the county clinics. In nearly all instances the same dose was employed in the repeat tests in the respective clinics. The tests were applied by physicians who were highly experienced in the field of tuberculosis and were read by the same physicians or public
health nurses who were also experienced in this field. The readings were recorded in accordance with the standards established by the National Tuberculosis Association. The tests were read at 48 and 72 hours after injection and were graded according to the widest diameter of induration.

- Negative — No induration
- One Plus — 6-10 mm. induration
- Two Plus — 11-20 mm. induration
- Three Plus — > 20 mm. induration
- Four Plus — Necrosis

The few doubtful tests were included in the negative readings. Repeat tests were carried out at three to six month intervals unless the physician in charge ordered otherwise.

Patient Care:

The diagnosis and management of the subjects remained the responsibility of the physicians in charge of the various clinics. In the county clinics, the subjects were divided into two groups on the basis of the family file number, the odd-numbered families were placed in the non-treatment groups, and the even-numbered families were placed in the treatment group. The treatment consisted of isoniazid, approximately 5 mg. per kilo per day administered in tablet form by mouth for a minimum of six months. A few were not treated at home but were sent to the sanatorium for care where they became patients of the sanatorium, and thus received varying treatment schedules in accordance with the physicians in charge. None of these latter patients are included among the reversion subjects.

Animal Studies:

Three groups of white guinea pigs were established, all weighing between 400—500 grams and in good health. They were all inoculated with 1.0 ml. of 0.1 mg. H37RV strain of M. tuberculosis. In group I, 23 animals were started on isoniazid (20 mg./animal/day) the day of inoculation. The drug was administered continuously in the drinking water and a dry feed was offered. Group II: 24 animals were started on the same dose of isoniazid 23 days following inoculation, and Group III: 24 animals received no medication. All of the animals were tested with old tuberculin, 0.1 ml. of a 1:20 dilution (5 per cent), intradermally, 21 days following the start of the experiment. Repeat skin tests were carried out at approximately three month intervals on five additional occasions between the start of the experiment on February 3, 1955 and the conclusion of the testing on May 13, 1956.

All of the remaining animals were autopsied at the conclusion of the experiment or at the time of death and gross findings in the spleen, liver, lungs, hepatic and tracheo-bronchial lymph nodes were evaluated and cultures were made of the spleen and lungs.

This report covers a two year period 1955-1957.

Results

At the present time there are 160 subjects under study who fit the criteria established. One hundred and twenty-one of these have been
followed by repeated tests (517) and 68 or 56 per cent of these have shown a change in their skin reactivity from a positive reaction to a negative one. Three hundred and thirty-three tests were performed on these 68 reverting subjects for an average of approximately five tests per subject. In Group A, infants under one year of age, there are 28 retested subjects and 17 of these have shown a reversal of their positive reaction. In Group B, there are 69 retested subjects who were initially negative and converted to a positive reaction within three months of the negative test; 40 of these individuals have changed to a negative test. In Group C, there are 24 retested subjects who were initially negative who became positive within 12 months. Of these, there are 11 subjects who changed to a negative test. The above data is recorded in the accompanying Table I.

In Figure 1, the subjects from all three groups have been arranged according to the degree of skin reactivity. The total number of individuals expressed in percentages is recorded on the ordinate. The curve shows the percentage of subjects reverting at the various levels of reactivity and falls in nearly a straight line from 76 per cent (35/46) at
one plus, to 50 per cent (15/30) at two plus, to 38 per cent (9/24) at three plus, to 17 per cent (1/6) at four plus. There were 8 individuals out of 15 who changed reactivity in whom no degree of positivity was expressed. These are shown as a separate point at 53 per cent.

The age of the subjects has not been restricted and varied from infancy to old age. However, 84 per cent of the patients are under 16 years of age, and 50 per cent are under 6 years of age.

As the study progressed, the untreated group became about twice as large as a group receiving treatment in the home. 16 individuals were transferred from clinic and home care to sanatoriums. Among this group of patients, there are no data available on reversals. Many of these have not been retested as yet. We do not wish to attempt to evaluate the effect of therapy at this time because of the inequality in the retesting procedures. This is not the objective of this paper, but is cited only to point out that the majority of the subjects with changes in their skin tests were not in the treatment group.

The reversal rate was found to be higher in the subjects who were tested with the 25 unit dosage of tuberculin (PPD) than with the 5 unit test dose. The reversal rate in the County Clinic patients (25 units) was 64 per cent, and in the city clinics (5 units) the rate was 38 per cent.

Results of Chest X-rays:

A total of 97 individuals were examined roentgenologically. Of these 63 were found to have a normal x-ray film study. The reversal rate in these subjects was 48/63 or 76 per cent. Thirty-four individuals showed findings which were interpreted as "positive," with 20 of these read as "presumably inactive," and 14 as "presumably active." Ten of the 20 subjects with inactive findings showed a reversal of their skin test. None of the patients with "active" findings showed a reversal of their tuberculin reaction. These findings tend to correlate well with the rate of change in skin reactivity, the individuals with negative chest X-ray films showing a high rate of reversal as opposed to those with positive findings with no change in the skin tests found in patients with findings which were read as "presumably active."

Results of Animal Studies:

The results of the experimental tuberculosis in guinea pigs is summarized in Table II. There were three groups of animals, the first received treatment from the start of the experiment, the second after three weeks and the third group was untreated. The results of skin testing with OT is correlated with time in the various groups.

Cultures of spleens were all negative in Group I. There were no gross findings of tuberculous lesions in the first group. In Group II, three animals had a positive spleen culture and one of the three animals had a positive lung culture. All other cultures were negative. Two of the three animals showed gross findings in the spleen, one in the lung and two had enlarged lymph nodes as well with small lesions demonstrable grossly. Group III animals all showed severe signs of tuberculosis. These results are comparable to those reported by Peizer, Chaves and Widelock in a much larger study. They showed no appreciable advantage in pre-treatment as opposed to treatment started simultaneously with infection,
but the immediate treatment method was found to be much more effective than when treatment was delayed for two weeks following inoculation.

The small animal study recorded here is presented to show a possible correlation of skin test reactivity with the severity of the infection. The treated animals never developed more than 1 to 2 plus reactions whereas the untreated animals developed plus 4 reactions uniformly.

**DISCUSSION**

The reversal of the tuberculin test is the primary reason for recording the data presented in this paper. It proved surprising in light of the traditionally held concepts regarding change in skin reactivity. Emphasis should be given to the fact that the subjects of this study were early converters with a known negative test unless the subject was an infant under one year of age. It has long been recognized that the majority of individuals who are infected by *M. tuberculosis* have little knowledge of when the primary illness occurred. It is possible that many primary infections are completely missed by our present methods of diagnosis of tuberculosis and because of the latent nature of the first infection. The use of the tuberculin test as a means of early diagnosis might be greatly increased if we were fully aware of its usefulness and reliability.

Dahlstrom in 1940 was one of the first workers to study what he chose to call “the unstable tuberculin reaction.” He showed the close relationship between the intensity of allergy and the probability of its ultimate disappearance as we have shown in this present report. When one considers that the reversal rate is definitely correlated with the degree of the initial reactivity, it suggests that the change may not be expressed in terms of “instability” as logically as it might represent a degree of recovery. The study of the patient from a true but minimal infection. On the other hand, we must seriously challenge the concept that reactions between 6 and 10 mm. truly indicate infection by *M. tuberculosis*.

The British Research Council recently analyzed a large group of adolescent children by comparing the various forms of tuberculosis in individuals reacting mildly (less than 15 mm. induration) to 3 tuberculin units as opposed to those reacting markedly to the same dose (greater than 15 mm. induration). The annual incidence of tuberculosis among the mild reactors was 0.78 per 1000 as compared to 2.53 per 1000 among the more marked reactors. In addition they reported a rate of 1.75 per 1000 of tuberculosis in those reacting positively to 3 T.U. as opposed to 0.74 per 1000 among those positive only to 10 T.U. and negative to 3 T.U.

Dahlstrom points out the importance of age and the overwhelming majority of “unstable reactors” among children who showed a much higher reversal than adults concerning whom he states “reversion to negative proved rare in adults.” Blatman, Rapmund, Newstran, and Alexander found a reversion rate of 54 per cent at 18 months in patients under three years of age. Their study was correlated with time and test dose rather than the degree of reactivity. When they used the largest commonly employed test dose of 1.0 mg. of OT, they found 40 per cent of the previously positive patients were negative. Although 50 per cent of the subjects in this study were under six years of age, no direct relationship of reversibility to age could

**TABLE II—RESULTS**

<table>
<thead>
<tr>
<th>Dates of Various Procedures</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/3/55</td>
<td>INH started</td>
<td>Skin test</td>
<td>Skin test</td>
</tr>
<tr>
<td>2/26/55 5+, 18—</td>
<td>24+, 0—</td>
<td>24+, 0—</td>
<td></td>
</tr>
<tr>
<td>2/26/55</td>
<td>INH started</td>
<td>23+, 0—</td>
<td>All strongly positive</td>
</tr>
<tr>
<td>5/6/55 13+, 9—</td>
<td>18+, 5—</td>
<td>18+, 5—</td>
<td></td>
</tr>
<tr>
<td>9/2/55 4+, 14—</td>
<td>19+, 0—</td>
<td>19+, 0—</td>
<td></td>
</tr>
<tr>
<td>11/4/55 8+, 8—</td>
<td>17+, 1—</td>
<td>17+, 1—</td>
<td></td>
</tr>
<tr>
<td>2/9/56 9+, 7—</td>
<td>17+, 0—</td>
<td>17+, 0—</td>
<td></td>
</tr>
</tbody>
</table>
be detected. The high rate may be related to age in part as 84 per cent of the subjects are children but the various groups are too small to permit critical analysis.

Early in the study, it became obvious that the value of repeating the skin test could not be overemphasized. We were continually surprised at the high incidence of negative tests in patients with previously positive reactions. The explanation is not clear but may represent fluctuations in sensitivity or healing of definite but slight infection with loss of reactivity. The low level and changing sensitivity after BCG vaccination would strongly suggest the latter mechanism. Whatever the answer to this question, it is apparent that greatly increased understanding will be had by repeating the tuberculin skin test. Many families have been greatly relieved when repeat skin testing and x-ray film studies have failed to confirm a previous diagnosis. A further understanding of the full meaning of positive and negative tests is badly needed and particularly the significance of weakly positive reactions. Although the tuberculin reaction remains one of the best tests in clinical medicine today, the interpretation of the plus one and two reactions must be challenged and further study continued. On the other hand, repeated testing may well represent a means of detecting tuberculous infection early and learning more about the natural history of this disease. Dubos* stated, "in this country, at least, few are the communities where tuberculin testing at short intervals of time is organized to permit the recognition of tuberculous infection in its initial phase."

SUMMARY

A certain proportion of 160 subjects with a previous negative tuberculin test who became positive reverted to negative when followed by repeated tests in direct relationship to the degree of reactivity. Sixty eight subjects including those positive under one year of age showed a change from positive to negative in 76 per cent when their skin test was one plus, 50 per cent when two plus, 38 per cent when three plus, and only one individual with a four plus reaction showed a reversal. The reasons for this surprisingly high rate of change are unknown, but may represent early detection of tuberculous infection in individuals who might otherwise go unrecognized at this stage of their disease. By repeated testing of known negative and positive subjects, the natural history of the disease may become better understood. It is apparent that further study of the tuberculin test is needed before its significance can be fully appreciated.

Roentgenological studies revealed a direct relationship of findings with the degree of change in tuberculin reactivity, the patients with negative chest x-ray films showed a high rate of reversal; in contrast, no change in skin reactivity was found where the findings indicated a "presumably active" lesion.

When infected guinea pigs were treated with isoniazid, their skin reactivity was reduced when compared to untreated controls. It treatment was begun at the time of inoculation, some animals failed to develop any positive reaction and all had negative cultures. If treatment was delayed, all developed weakly positive skin test reactions and a few showed signs of tuberculosis at autopsy and by culture.

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RESUMEN

Cierta proporción de 160 individuos con previa reacción tuberculínica negativa y que se volvieron positivos, retornaron a la negatividad cuando se les siguió observando con repetidas pruebas, en relación directa con el grado de reactividad. Sesenta y ocho sujetos incluyendo niños que fueron positivos, menores de un año de edad, mostraron un cambio de positivo a negativo en 76 por ciento cuando su prueba cutánea era de una cruz, 50 por ciento cuando era de dos cruces, 38 por ciento cuando eran de tres cruces y sólo en uno de cuatro cruces se observó esa reversión. Se desconocen las causas de esta elevada proporción de cambios, pero puede representar una temprana detección de infección tuberculosa que de otro modo pasarían sin reconocerse en esta etapa de la enfermedad.

Por la repetida prueba de los negativos conocidos y positivos, la historia natural de la enfermedad puede comprenderse mejor. Aparentemente se necesita un estudio ulterior de la pruba tuberculínica para que su significación se conozca completamente.

Los estudios roentgenológicos revelaron una relación directa de hallazgos con el grado del cambio de la reactividad tuberculínica; los enfermos con películas negativas mostraron mayor frecuencia de reversión; por el contrario no se encontró cambio en
la reactividad cutánea cuando los hallazgos radiológicos indicaron una lesión "probablemente activa."

Cuando los cuyes infectados fueron tratados con isoniazida, su reactividad cutánea se vio reducida al compararse con los controles no tratados.

Si el tratamiento se empezó al tiempo de la inoculación algunos animales dejaron de presentar reacción positiva y todos tuvieron cultivos negativos. Si el tratamiento fué diferido, todos desarrollaron reacciones cutáneas débiles positivas y pocos mostraron signos de tuberculosis a la autopsia y por cultivo.

RESUME

Sur 160 individus ayant viré leurs réactions tuberculiniques, un certain nombre eurent de nouveau des réactions négatives après des examens répétés. Cette modification se produisit d'une façon tout à fait parallèle à l'importance qu'avaient eu les réactions. 60 sujets, comprenant des bébés ayant leurs réactions positives avant l'âge d'un an, eurent de nouveau des réactions négatives dans 76% des cas, quand leur réaction cutanée était légèrement positive (+) la négativation secondaire apparaît dans 50% des cas quand elle était un peu plus positive (+++) dans 38% lorsque la réaction était nettement positive (++++) et chez un seul individu porteur d'une réaction très positive (+++). Les raisons de ce taux considérablement élevé de retour à la négativité sont inconnues, mais cela être en rapport avec une détection précoce de l'infection tuberculeuse chez des individus qui autrement continueraient à être ignorés à ce stade de leur affection. En répétant les examens sur des sujets dont les réactions, on finit par mieux comprendre l'histoire de l'infection.

Il semble que des études ultérieures sur le test tuberculinique soient nécessaires avant que sa valeur puisse être parfaitement appréciée.

Les examens radiologiques montrèrent une relation évidente avec l'importance du retour à la négativité des réactions tuberculiniques: les malades ayant des clichés négatifs présentèrent un taux élevé de négativation; au contraire, aucune modification dans les réactions cutanées ne fut décelée quand les constatations radiologiques indiquaient une lésion "probablement active."

Chez des cobayes qui ont été traités par l'isoniazide, leurs réactions tuberculiniques diminuèrent en intensité comparativement à celles des témoins non soumis au traitement. Si le traitement est commencé au moment même de l'inoculation, quelques animaux ne présentent pas de réactions tuberculiniques positives, et tels donnent des cultures négatives. Si le traitement est différé, tous avaient des réactions cutanées tuberculiniques faibles, et un petit nombre d'entre eux présentent des manifestations de tuberculose à l'autopsie et à la culture.

ZUSAMMENFASSUNG

Es wurde ein bestimmter Prozentsatz von 160 Personen mit zuvor negativ gewesener Tuberculinreaktion, die positiv geworden war, wiederum negativ, wenn sie durch wiederholte Teste weiter beobachtet wurde in direktem Verhältnis zum Ausmass des Reaktionsvermögens. 68 Personen einschließlich Kleinkinder, die während ihres ersten Lebensjahres positiv waren, zeigten einen Umschlag von Positiv zu Negativ in 76%, sofern der Hauttest positiv war, in 50%, wenn er zweifach positiv war, in 38% wenn er dreifach positiv war und nur ein Fall mit einer Reaktion von Stärke 4 zeigte einen Umschlag. Die Gründe für diese überraschend hohe Umschlagrate sind unbekannt; aber es ist so die frühe Entdeckung der tuberkulösen Infektion bei Personen möglich, die am Ende dieses Stadium ihrer Erkrankung unerkannt bleiben. Durch wiederholte Testung bei bekannten negativen und positiven Personen lässt sich der natürliche Ablauf der Erkrankung besser verstehen.


REFERENCES


