

Original Articles.

THE TUBERCULIN TREATMENT OF DISPENSARY PATIENTS.

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THE therapeutic use of tuberculin has met with but little favor among the majority of medical men up to the present time. Deep-seated prejudice as the result of its previous abuse, and failure to appreciate its value in the hands of those who know its dangers and limitations, is in large degree responsible for this. Along with the rapid increase of special clinics for tuberculosis and the present active interest in all branches of this subject, however, a far wider use of tuberculin may be expected. In certain German clinics for consumptives, notably that under the direction of Hammer at Heidelberg, tuberculin is used in almost every case. Not only in incipient but also in advanced cases it has been found to be of value. Hammer, indeed, believes that all stages of pulmonary tuberculosis are benefited by tuberculin; in advanced cases it may not produce lasting effects, but will undoubtedly prolong life and alleviate distressing symptoms. This, too, has been our experience. But it is in the incipient stages of pulmonary disease and in so-called "surgical" tuberculosis, whether of bones, glands, joints or elsewhere, that tuberculin will do the most good. Raw, of Liverpool, basing his observations on 1,600 cases of surgical tuberculosis, says that his results have been successful beyond his anticipations.

While it is undoubtedly true that to get the best results from tuberculin patients should be under close observation in some institution, this is not absolutely necessary. Hammer believes that when tuberculin is used in a cautious way among dispensary patients all harm may be avoided, with comparatively little interference with the patient's business. Likewise, Raw believes it can be given with safety and benefit to patients outside of sanatoria and hospitals, and advises practitioners "to treat their tuberculosis cases with tuberculin in their own homes." Our own patients have been of this type, living at home during the entire course of treatment. Eighty have been members of our Suburban Tuberculosis Classes. Here, by means of weekly meetings of the class, home records of pulse, temperature and daily life, and visits in the homes by our nurse, we have been able to keep our patients under strict supervision; the remaining 63 patients have attended the dispensary of the Boston Consumptives' Hospital or the day camp of the Good Samaritan Hospital.

Tuberculin has been only one factor in the treatment of these patients. Particularly in the cases of pulmonary tuberculosis, we have tried to build up the general health by fresh air, food and rest. In many instances, tuberculin treatment has been but an adjunct, distinctly subordinate to an open-air hygienic life; in others,

especially where the general condition of the patient was excellent and the disease a purely local process, we feel that tuberculin has been the important factor in bringing about any improvement which has taken place. Denys has recently reported that out of 470 patients in all stages of phthisis attending his clinic, 71% have recovered or improved greatly. These good results he ascribes entirely to tuberculin, as in only very few instances was it possible to make any radical change in the patients' mode of living. Our own feeling is more conservative. We are strongly of the opinion that, properly handled, tuberculin will do a great deal of good, but we are equally firm in believing that the least we can do is to see that it does no harm; and, finally, that in the vast majority of cases it should be used only as an adjunct to sanatorium methods.

We have been most fortunate in our work in having the constant help and advice of Dr. Edward L. Trudeau. He has been interested in our endeavor to show that tuberculin by itself is beneficial to patients without the aid of climate or of a strict sanatorium régime. He writes as follows:

"I have watched your work with tuberculin in dispensary practice with the utmost interest, and your results are quite as good as I thought it possible they would be under the conditions of environment of your patients. In my advocacy of the value of tuberculin treatment based on my own experience of its use for many years, I have always been met with the objection that my results were due to favorable conditions of environment and not to the specific action of the tuberculin. This was an objection that I could not answer, although I felt certain of the therapeutic value of the tuberculin injections. Your work is a valuable addition to our knowledge of the subject because it shows that the curative influence of tuberculin on the disease is sufficiently marked to make it of use in its treatment among the many who cannot add to it the well-established beneficial influences obtainable from the climatic and open-air method. Any treatment that will influence tuberculosis favorably in that great mass of people who cannot leave their work and surroundings is a distinct advance, and I am particularly struck with the excellent results you get in pulmonary tuberculosis and tuberculous adenitis in children, and also in bladder cases, a form of tuberculosis which usually is little benefited by any kind of treatment. The great objection to the general application of tuberculin treatment in cities is that it requires patience and skill in its administration, and that if carelessly used it may be injurious. That it need not be injurious is one of the valuable facts which your work brings out.

"Tuberculin treatment, as we know it at present, either produces a partial immunization to the proteid substances of the tubercle bacillus, or at any rate stimulates the defensive resources of the system when it is not already overwhelmed, as in the case of active types of the disease, and I feel, as I have felt for many years in spite of the

bitter opposition to its use, that it is a valuable aid to the treatment of certain forms of the disease. Your work brings evidence that the lives of thousands of cases of incipient tuberculosis, and even of advanced cases, when chronic in type, as well as those suffering from surgical tuberculosis, may in many instances be saved and prolonged by this treatment without any change in their surroundings.

"When we realize that less than 10% of all cases of tuberculosis can leave their surroundings and go to sanatoria, the importance of any specific treatment which offers any prospect at all of cure without change of surroundings or occupation is evident. Of course the early detection of the disease and the evident limitation of the advantages of tuberculin treatment to the chronic types of the disease must always be borne in mind."

We have tried to follow the rules which Dr. Trudeau has formulated for the safe administration of tuberculin. These are in brief:

1. To begin treatment with very minute doses.
2. To raise the degree of tolerance to the highest attainable point by a long-continued progression of dosage.
3. To avoid general and local reaction as much as possible, regarding them merely evidence of intolerance.
4. To follow no arbitrary rules as to the rate of increase or the maximum dose to be reached, but to be guided merely by the degree of toxin tolerance in the individual case.

KIND OF TUBERCULIN. METHODS OF PREPARATION AND ADMINISTRATION. DOSAGE.

There is much difference of opinion in regard to the best kind of tuberculin for therapeutic purposes. Spengler and Raw believe in the superior immunizing power of bovine tuberculin against human tuberculosis, especially in surgical forms of the disease. Denys is a strong believer in the bacillary filtrate as an immunizing agent. Hammer still favors the use of old tuberculin. For most of our patients we have used the bouillon filtrate kindly provided by Dr. Trudeau. In a few cases old tuberculin has first been given, followed later by the bouillon filtrate; in other instances we have used equal quantities of dilute bacillen emulsion and bouillon filtrate. In surgical tuberculosis this combination seems to be the most effective.

The crude tuberculin must be diluted into solutions of various strengths. This is a comparatively simple process, but one which demands absolute accuracy. The dilutions vary according to the kind of tuberculin employed. The bouillon filtrate which we have used in most of our cases is diluted by .25% carbolic acid into six solutions ranging from No. I, of which 1 ccm. contains .0001 mgm. of tuberculin, up to No. VI, of which 1 ccm. contains 10 mgm. of tuberculin. These dilutions are made fresh every two weeks, using a 1 ccm. graduated glass pipette. In most instances the initial dose has been .0001 mgm., or 1 ccm. of solution No. II. In a few cases of ocular tuberculosis we have found even

this too strong and have given .00001 mgm. or 1 ccm. of solution No. I. By means of a special tuberculin syringe it is easy to give such small amounts of fluid as 1 ccm. with perfect accuracy. At first, when doses are very small, patients are given two injections a week; as the doses increase in size, however, they receive tuberculin only once a week. In most instances we have increased the doses according to Dr. Trudeau's methods — .1, .2, .3, .4, .5, .6 ccm., etc., of the first solution until 9 ccm. is reached, and then begin with .1 ccm. of the next stronger solution. In a few chronic cases we have increased the doses faster than this. We have tried to regard each patient as an individual problem and to give the dose suited to that particular case. As long as tolerance is maintained doses are gradually increased according to this method until 10 mgm. are reached. This usually takes six months to a year. Many patients get discouraged and drift away before this time.

REACTIONS.

Reaction to tuberculin may be of three types, local, focal and general. A local reaction occurs at the site of inoculation; a focal reaction occurs in the tuberculous focus itself. The symptoms of the former generally appear eight to twenty-four hours after the injection and last a few days. The symptoms of a reaction at the site of the tuberculous process naturally depend on the character of the lesion. If there is tuberculosis of the lungs, cough and expectoration will increase and, on examination, râles will be found to be more numerous. If the bladder is involved, there will be increased frequency, pain and perhaps hematuria; if it is a tuberculous joint, there is increased swelling, redness, etc. One or two or all of these signs and symptoms may be present. If after each injection careful inquiry is made, and if the warning given by these milder symptoms is heeded, a dangerous severe reaction may be avoided. A local reaction alone frequently occurs when the patient is on the border line of intolerance; when there is a general reaction, however, local symptoms are practically always present.

The most important evidence of a general reaction is a sudden rise in temperature. This as a rule appears in about eight to twenty-four hours after the injection and may last several days. Associated with this there is apt to be nausea, vomiting, headache, chills, chilly feelings and general malaise. After each injection we study the patient's home record book for any such rise of temperature and make careful inquiry of the patient himself for any signs or symptoms of reaction, local or general. If there is any evidence of intolerance, however slight, we omit the next dose of tuberculin, give a smaller dose or repeat the same dose according to circumstances. The few reactions we have had were of a very mild type. In many instances tuberculin has been given for over a year without reaction. In certain cases of tuberculous adenitis and ocular tuberculosis marked improvement has followed a mild reaction, and in such rare instances we have given

larger doses than usual so as to cause such reactions. This, however, has not been our usual custom.

It often happens that patients attribute to tuberculin certain symptoms occurring after an injection which in reality had nothing to do with the effects of the tuberculin. Dr. Trudeau has seen several cases when patients developed acute miliary tuberculosis, meningitis or hemoptysis a few days after they were to have taken tuberculin but for some reason did not. We have had one such case. One of our patients had reached the dose of 1 mgm. of bouillon filtrate without reaction. Two days after the last injection he developed meningitis and died. Subsequent study of the case showed that in the forty-eight hours following the last injection there had been no rise in temperature nor any sign of a reaction, local or general; no evidence whatsoever could be found to suggest that this development of a fatal meningitis was anything more than a coincidence.

SELECTION OF PATIENTS.

In surgical tuberculosis we have used tuberculin as a routine measure. In many patients it was the only treatment; in others it was used to supplement the improvement which we were able to make in the patient's mode of living. Many patients attended other departments of the hospital for local treatment. In pulmonary tuberculosis, our use of tuberculin has been confined to children in the closed stage of the disease, afebrile early adult cases, and certain chronic advanced cases. Recent hemorrhage we have considered a definite contra-indication. A certain degree of intelligence and a willingness to co-operate on the part of the patient is not only desirable, but necessary if one is to get good results.

PULMONARY TUBERCULOSIS.

In our tuberculosis classes at the Massachusetts General Hospital since October, 1905, we have treated 34 phthisical patients with tuberculin. Of these, 17 were incipient, 3 moderately advanced and 14 advanced. Of these latter, 10 have died, 2 have made marked improvement and 2 have remained stationary. Of the 10 who died only 5 were in the class long enough to undergo a complete course in tuberculin. We feel that these 5 patients were helped by the tuberculin, in that cough and pain were relieved, the amount of sputum decreased and life prolonged and made more comfortable. All but 2 of the 17 incipient cases were children under fifteen years of age with so-called closed tuberculosis. These patients are now all in excellent health one or two years after their tuberculin treatment. How much of this improvement is due to changed habits and surroundings, how much to the natural resistance and growth of the child, and how much to tuberculin, it is hard to say. It has been our experience that, unless the patient has a certain amount of natural resisting power of his own, tuberculin will be of little value.

In addition to these patients treated in our

tuberculosis classes, we have been able to follow two series of patients attending the Good Samaritan Day Camp. One group received tuberculin, the second series was treated at the camp without tuberculin. Of the 46 patients who received tuberculin, 12 were incipient, 17 were in the second and 17 in the third stage. Of these, 32 were discharged arrested, 7 improved and 7 unimproved. Six of the arrested cases have relapsed after a period of from one year to two years and nine months since leaving the camp. Of the 7 patients discharged improved, 2 have died and the condition of the others is poor. Of the 7 patients not improved by camp or tuberculin, all are dead. The maximum doses of tuberculin these patients received varied from .02 mgm. to 8 mgm. T. R. Some of those who received the highest doses have relapsed, whereas those who received smaller amounts have remained well, emphasizing the fact that the effects of tuberculin vary greatly in different individuals.

Of the second series of 42 patients who did not receive tuberculin, 15 were in Class I, 16 in Class II, and 11 in Class III. Thirty of these patients were discharged arrested, 5 improved and 7 unimproved. Of the 30 arrested cases, 5 have relapsed; of those improved, 1 is dead and the others are in poor condition, while of the 7 unimproved, 3 have died. The time since these patients left the camp varies from three to twenty-one months. The only difference in the results obtained from the treatment of these two series of patients, one with and one without tuberculin, is in the length of time before relapses occurred. In the first group of 32 patients discharged arrested, there were 6 relapses in one to two and one-half years; in the second group of 30 arrested cases treated without tuberculin, 5 relapsed in four to twenty-one months. In other words, about the same number of patients relapsed without tuberculin as with it, but in a much shorter time.

TUBERCULOSIS OF THE EYE.

These patients have been referred to us by Dr. George S. Derby from his clinic at the Massachusetts Charitable Eye and Ear Infirmary and at the Carney Hospital. He has made the diagnosis of the eye condition. In every instance there was a positive skin or eye tuberculin reaction, while in at least 80% of the cases, on a careful physical examination made by one of us, there was plain evidence of active or arrested tuberculosis elsewhere. Many of these patients were advancing to total loss of sight; many had not only failed to improve under local treatment of the eye, but had suffered frequent relapses. Dr. Derby sent these patients to our classes primarily for instruction in hygiene, etc., and second for specific treatment with tuberculin. He writes as follows:

"For over two years I have had the privilege of referring cases of ocular tuberculosis to the tuberculosis classes conducted at the Massachusetts General Hospital, and have availed myself of this to a very large extent because our eye clinics have but small facilities for treating these

patients efficiently. Although the time is too short and the number of observations too small to allow us to give any accurate statistics as to results, yet there is no doubt in my mind as to the superiority of the class methods over our old methods of treatment. It has been the greatest satisfaction to watch the marked and steady improvement in these most intractable cases."

We have had 25 such patients under observation for periods of from three years to three months. With one or two exceptions there has been marked improvement not only in the local process in the eye, but also in the general condition. In many patients there has been a great improvement in vision; in others, chronic recurrent conditions have cleared up, and in nearly all a process which was getting progressively worse has at least been arrested. The majority of these patients made no very radical change in their methods of living. If a patient was under weight he was built up; fresh air at night was demanded, and a certain number of hours outdoors each day as the case might require. Some gave up work and devoted all their time to the treatment. All received tuberculin. We feel that here specific treatment has been a much larger factor in bringing about good results than it was in the pulmonary cases.

We found the eye very susceptible to tuberculin, having seen marked reactions to .00001 mgm., an almost inconceivably small dose. In one patient we were unable to go beyond this amount because of the severity of the reaction following every attempt at increase. In a few cases where there seemed to be no improvement under the regular rate of progression we purposely increased the dose so as to cause a mild reaction and have seen good results from so doing. This, however, is not our usual custom.

TUBERCULOUS ADENITIS.

We have treated with tuberculin 20 patients of this class for a sufficient length of time to be able to judge as to results. Ten were under sixteen years; the oldest was twenty-eight years. Two had pulmonary involvement, 1 had an empyema with a discharging sinus, 1 had a tuberculous peritonitis, 1 tuberculous keratitis and 1 tuberculous of the fascia of the upper arm. Tuberculin has been the most important factor in the improvement these patients have shown. The general condition of most of these patients was so good that little if any change was made in their mode of life. Some had discharging sinuses which had failed to heal despite careful surgical attention. Several had had extensive operations followed by a recurrence of the glands. In such conditions as this tuberculin seems to have had an almost specific effect. Of these 20 patients, the one with peritonitis died; the remaining 19 showed very marked improvement and are now in excellent condition. Larger doses of tuberculin can be used here than in other forms of the disease. Improvement is much more rapid in children than in adults. In adults, tuberculin seems rather to

wall off and encapsulate the glands than to cause them to disappear.

GENITO-URINARY TUBERCULOSIS.

We have had under treatment 5 patients with tuberculosis of the kidney, ureter or bladder. Three had had a tuberculous kidney removed, leaving traces of the disease in the ureter, bladder or both; one, after removal of the left kidney, began to show signs of the disease in the remaining kidney and in the bladder. Her condition now, two years after beginning treatment with tuberculin, is apparently one of perfect health; a slight recurrent hematuria is the only indication that anything is wrong. She is at her maximum weight, with normal temperature and pulse, and she feels well in every respect. We believe that tuberculin has played an important part in localizing the disease and preventing its progress. The other patients are now in excellent condition and at work.

LUPUS.

Three patients with lupus have been under treatment with tuberculin. In one there was no change, the second made a slight improvement and the third made marked improvement. These patients were under treatment from six to fourteen months. Our experience accords with that of others that lupus seems to react very poorly to tuberculin.

BONE AND JOINT TUBERCULOSIS.

We have had 4 cases of bone or joint tuberculosis under tuberculin treatment. One had tuberculosis of the scapula, sternum and ribs with discharging sinuses of a very obstinate nature; 1, tuberculosis of the wrist; 1, tuberculous disease of the foot and elbow; and 1, tuberculous dactylitis. This last patient, a baby two years old, has made marked improvement and to-day shows no deformity. The first patient is absolutely well and the others improved. Bone tuberculosis is very resistant to tuberculin treatment, probably because of the dead bone; until this is removed, progress is bound to be slow.

TUBERCULOSIS OF THE LARYNX.

We have not included in this series those cases where the disease was but a late complication of advanced phthisis, but only those in which it was a localized process in the throat without pulmonary involvement. We have had two such patients under treatment for eight and ten months respectively. In each at the first examination there were suspicious signs in the lungs, which, however, soon disappeared. In one patient the throat condition has shown only slight improvement; in the others there has been a marked change for the better. The general health of each patient is vastly improved. In neither case was any very great change made in the mode of living, so that whatever improvement there is may justly be attributed to tuberculin.

MILIARY TUBERCULOUS PERITONITIS.

We have recently had three patients with tuberculous peritonitis under tuberculin treatment; their rapid improvement since this treatment was begun has been very marked.

SUMMARY OF CASES AND RESULTS.

Pulmonary Tuberculosis.

Number of cases,	80
Class I, incipient,	29
Class II, moderately advanced,	20
Class III, advanced,	31
Apparently cured or arrested,	43 (53.7%)
Improved,	9 (11.3%)
Not improved,	9 (11.3%)
Dead,	19 (23.7%)

Tuberculosis of the Eye.

Number of cases,	27
Improved,	25
Not improved,	2

Tuberculous Glands.

Number of cases,	20
Improved,	18
Not improved,	2

Genito-Urinary Tuberculosis.

Number of cases,	5
Improved,	5
Not improved,	0

Tuberculosis of Bones and Joints.

Number of cases,	3
Improved,	2
Not improved,	1

Lupus.

Number of cases,	3
Improved,	2
Not improved,	1

Tuberculous Peritonitis.

Number of cases,	3
Improved,	3
Not improved,	0

Tuberculosis of the Larynx.

Number of casts,	2
Improved,	1
Not improved,	1
Total number of cases,	143
Improved,	108 (75.5%)
Not improved,	16 (11.3%)
Dead,	19 (13.2%)

It is evident that the different forms of tuberculous disease show wide variations in regard to their response to tuberculin treatment. From our experience with tuberculin so far, we would classify the forms of tuberculosis in regard to the effects of tuberculin as follows:

1. Forms of Tuberculous Disease Favorable to Tuberculin:
 - a. Incipient pulmonary tuberculosis, especially in the closed stage in children.
 - b. Chronic advanced pulmonary tuberculosis.
 - c. Tuberculous adenitis in children.
 - d. Tuberculosis of the eye.
 - e. Genito-urinary tuberculosis.
2. Forms of Tuberculous Disease Less Favorable to Tuberculin:
 - a. Febrile advancing pulmonary tuberculosis.
 - b. Tuberculous adenitis in the adult.
 - c. Bone tuberculosis.
 - d. Lupus.
 - e. Tuberculosis of the larynx.

It is important to remember that in no instance have any of these patients been inmates of a sanatorium, hospital or other institution while under treatment by us. They have lived in their own homes and, in many cases, have continued at their work. Despite these adverse conditions, however, our results with tuberculin on the whole have been favorable and have decided us to continue its use.

SUMMARY AND CONCLUSIONS.

1. Out of 143 patients with various forms of tuberculosis treated with tuberculin during the past four years, 19 have died, 16 have shown no improvement, while 108 have been benefited to a greater or less degree.

2. In no instance have we been able to see that tuberculin has done the slightest harm; reactions have been rare and invariably of a very mild type.

3. In incipient pulmonary tuberculosis, especially in children, tuberculin is a factor in increasing body resistance and in maintaining this resistance so as to prevent relapses. In more advanced pulmonary disease tuberculin will often alleviate distressing symptoms, prolong life and occasionally help to arrest the process.

4. In localized or "surgical" tuberculosis, tuberculin has a marked beneficial effect. Its administration should always be combined with hygienic outdoor treatment, and in the vast majority of instances should be subservient to this.

5. Dispensary patients can be treated with tuberculin not only with perfect safety, but with benefit, providing that there is a close personal co-operation between patient and physician.

THE THERAPEUTIC ADMINISTRATION OF TUBERCULIN IN SURGICAL TUBERCULOSIS.

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ALTHOUGH we have little knowledge of immunity to the tubercle bacillus, and although it has been shown by Theobald Smith¹ that tuberculin furnishes no immunity against infection in calves, yet there is considerable clinical evidence that it is helpful in the treatment of human tuberculosis. As most of this knowledge has been gleaned from its use in pulmonary tuberculosis, it may be desirable to state our results in the employment of tuberculin in glandular lesions where the action can be more readily followed.

Most of our cases have been tuberculosis of the cervical lymphatic glands. The diagnosis has been made clinically, and in some confirmation has been sought by the skin reaction of von Pirquet. So far as it was possible to determine, the lungs and viscera in all were not affected. All the patients have been referred to us from the Out-Patient Department of the Massachusetts General Hospital. They have had no other treatment than the simple hygienic rules which could be

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