Streptomycin in the Treatment of Tuberculosis in Children*

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Streptomycin has been developed into an extremely important place in the treatment of tuberculosis. The medical literature is replete with articles dealing with streptomycin in the treatment of tuberculosis in adults but few articles have appeared concerning the use of this antibiotic in treating tuberculosis in children. Because of the tendency of the past 15 years to pay less attention to the child with primary tuberculosis and to close many of the previously well-occupied children's units in sanatoria throughout the country, it might be expected that streptomycin would find a very insignificant role in this phase of tuberculosis work. However, there are still children with more than the simple primary tuberculosis who require more than an occasional clinic checkup while on a limited exercise routine at home: there are still a fair number of children whose tuberculosis is not confined to hilar nodes, who require sanatorium care and definite therapy. It is these children who provide a place for the use of streptomycin.

At Maybury Sanatorium Children's Unit, streptomycin was made available for emergency cases in April 1947, for research purposes in August 1947, and for all purposes in October 1947. From April 22, 1947 to January 31, 1949, 101 of our 281 children received streptomycin. A review of these children with five months' follow-up in comparison with a similar series comprising 780 children treated in the six-year period from January 1, 1941 to December 31, 1946, forms the basis for this presentation. There is no essential difference in the treatment of the two groups except that streptomycin was used in the 1947-49 group. The same system of classification and the same method of evaluating the results was used in both groups. Streptomycin was not used in the simple primary tuberculosis cases because they have a tendency to recover without treatment and the hazards of streptomycin therapy did not justify its use. The 101 cases treated with streptomycin are divided roughly into the following groups: 1) miliary and meningitis, 2) severe primary, 3) primary with bronchial complication (PBC), 4) re-infection tuberculosis, and 5) extrapulmonary tuberculosis. Streptomycin therapy varied in the different groups and several changes in dosage were made during the period of this study. Of the 101

*From the Wm. H. Maybury Sanatorium, Northville, Michigan.
children, 22 had part or all of their streptomycin before transfer
to Maybury Sanatorium. We are not presuming to outline the ideal
method of using streptomycin but are merely presenting our
observation of 101 streptomycin- treated tuberculosis children and
describing our present method of administration.

**Miliary and Meningeal Tuberculosis**

Miliary and meningeal tuberculosis constituted the emergency
cases for which the early supply of streptomycin was hopefully
allocated. It has been noted that this form of tuberculosis provided
a prime indication for streptomycin therapy.\(^1\)\(^2\) Infrequently had
there previously been recoveries observed. Of the 50 miliary cases
treated during the 1941-46 period only 13 recovered. The recoveries
here occurred only in the coarse type but never in the fine miliary
cases. Although the fine miliary cases are more likely to develop
meningitis it was found to be a common occurrence also in children
with coarse miliary lesions.

Miliary tuberculosis is prone to develop in the severe primary
and the progressive primary type of case. The sooner streptomycin
therapy can be instituted the better are the chances of good
results. Even in those children who are potential miliary cases and
who show a definite aggravation of toxemia without obvious cause,
one should suspect beginning miliary spread and institute strepto-
tomycin therapy. Children, even very young children, tolerated streptomycin well—better than adults.

Large doses of streptomycin are indicated in miliary and menin-
geal tuberculosis. After early schedules were modified by reason
of our experience and information received from other workers
in the field,\(^3\)\(^4\) a dosage formula based upon body weight was
developed. For miliary tuberculosis it is as follows: 55 to 88 mg.
streptomycin per kilogram (25 to 40 mg. streptomycin per pound)
per day for three to six months depending upon the occurrence
of a definite recession of the disease and then 25 to 44 mg. per
kilogram (10 to 20 mg. per pound) per day for the remainder of
the six months period. The severity of the case is used to determine
the exact dosage within the formula. The daily amount is divided
into two or three doses depending upon the quantity of solution
to be injected at each time and the size of the patient. Our standard
streptomycin solution is 200 mg. to 1 cc. of water: 1.5 cc. is about
the maximum injection which a small child will tolerate.

Six questionable miliary* cases were also treated and four of

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* Miliary tuberculosis was classified as questionable when the roentgeno-
gram taken at the clinical onset of the miliary episode showed fairly
well defined miliary lesions which were not confirmed by subsequent
roentgenograms, streptomycin having been administered in the mean-
time.
these have no response to the caloric test. These 18 children are alive and doing well. All have completed their course of streptomycin and gastric cultures are negative for acid fast bacilli. Three of the miliary and four of the questionable miliary cases have been discharged to their homes. Three children whose miliary lesions were advanced were left with miliary fibrotic nodules but without accompanying clinical manifestation of miliary tuberculosis. Relatively few acute toxic manifestations were experienced in this group but lack of nystagmus to the caloric test developed in nine of the 12 miliary cases treated and five of these nine also had objective evidence of dizziness.

Meningitis

Four additional cases of miliary tuberculosis were given streptomycin therapy but there was an associated meningitis and these cases are considered with the nine children who comprise the meningitis group. Two of these developed meningitis while they were under streptomycin therapy for miliary tuberculosis. One of these had an extremely fine miliary and normal spinal fluid when intramuscular streptomycin was started. After meningitis developed he was given intrathecal streptomycin in addition to the intramuscular; the total course covered a six months period. The other child was admitted at one year of age with an advanced but coarser miliary superimposed upon a consolidated upper lobe which was excavating. Spinal fluid was normal at the beginning of streptomycin therapy. Three months later intra-thecal streptomycin was added but was not well tolerated. The intramuscular dose was increased from 60 to 96 mg. per kilogram per day. She had 151 gm. of intramuscular streptomycin in 249 days and 312 mg. of intrathecal streptomycin in 156 days. The miliary lesions became fibrotic, the pneumonic process improved but the spinal fluid findings remained positive for tuberculous meningitis and the cultures continued to be intermittently positive for acid fast bacilli. She was able to stand in her crib and take fluids until a week before she died although irritability, vomiting, and weight loss were progressive. Opisthotonos and increasing elevation of temperature up to 109 degrees F., terminal fever developed and death occurred seven months after the onset of meningitis and ten months after the start of streptomycin therapy. Of the 101 streptomycin treated children this is the only one who died at Maybury Sanatorium.

Besides the four meningitis patients who had associated miliary tuberculosis, three other children had associated extrapulmonary tuberculosis and two had associated active primary tuberculosis. In only one of these nine children were the symptoms of menin-
gitis severe when streptomycin was started. He was irrational on transfer from a general hospital. One other was admitted to the sanatorium with an advanced miliary and early meningitis. The other seven developed meningitis while in the sanatorium and streptomycin therapy was instituted before the symptoms had reached the stage that one would ordinarily have suspected the disease. The diagnosis of tuberculous meningitis was in all cases confirmed by laboratory tests on the spinal fluid.

After some variation of dosage in the early cases the following formula of streptomycin therapy was established for tuberculous meningitis: i.e., intramuscularly 55 to 88 mg. per kilogram of body weight per day for four to six months depending on the clinical and spinal fluid response and then 22 to 44 mg. per kilogram per day for the remainder of the six months period. Intrathecal streptomycin 2.5 mg. per kilogram per day (up to 50 mg.) is given for three weeks, then the same dose three times per week for three months, and then one-half that dose twice a week for two months. If intrathecal streptomycin could not be given the intramuscular dose was increased to 100 mg. per kilogram per day. The intrathecal injections were given after the spinal pressure had been reduced to normal by withdrawal of fluid, the proper amount of streptomycin was injected in 5 cc. of water.

Five children, now 26 to 19½ months after the onset of meningitis, have recovered and gone home. One, as mentioned above, is deceased. The three who remain in the sanatorium are free from symptoms and spinal fluid findings of meningitis. All have completed the streptomycin course. One child who had associated tuberculosis of the dorsal spine received no intrathecal streptomycin and two others had less than 10 intrathecal doses. All nine children have loss of equilibrium by the caloric test but have compensated well. One child, the first case, became deaf.

There is still some controversy over the use of intrathecal streptomycin in treating cases of tuberculous meningitis, one argument against its use being that streptomycin is a very irritating substance and, therefore, likely to produce neural damage. However, it is known that meningitis develops in children receiving streptomycin by intramuscular injection—two such cases are included in this series—therefore, it would seem that something more than intramuscular streptomycin was needed in treating the condition. Levinson reports 11 deaths in 19 children treated by intramuscular streptomycin alone.5

In the series of cases treated prior to streptomycin 39 had meningitis and all 39 died within a month after the condition was diagnosed. There is no possibility of comparing the condition of these recovered meningitis children with those not treated with
streptomycin and, therefore, it may be that at least some of the neural damages are due to the meningitis and not altogether to the drug. In our experience there is also no evidence to support the claim that intrathecal streptomycin produces either a greater incidence or a more profound type of vestibular damage than large intramuscular doses alone.

**Severe Primary Tuberculosis**

Severe primary tuberculosis with extensive parenchymal involvement in small children provides a definite indication for streptomycin therapy. The simple primary cases have a tendency to recover spontaneously. They can well be handled in the home. Streptomycin is not indicated in these children but they must be followed carefully for signs and symptoms of exacerbations of the primary or complications such as miliary, bone and joint, or other tuberculosis. The child who has primary tuberculosis and symptoms of pneumonia may have either a superimposed non-tuberculous infection or an acute increase in his tuberculosis. If a trial of penicillin and other measures does not result in prompt clinical and x-ray improvement one should not hesitate to start streptomycin. The formula for therapy in these cases is as follows: 33 to 66 mg. per kilogram of body weight per day for four to seven days or until there has been a satisfactory effect, then one-half that dosage three days a week for the balance of 42 doses. The determination of the number of daily doses and the size of the individual injection is made again on the basis of the size of the child and the maximum dose of a 200 mg. per cc. solution which he would tolerate. The response to streptomycin will in most cases be quite prompt so that after four to seven days the initial concentrated therapy may be reduced. Even though the clinical progress may be excellent, one must not forget the possibility of these cases developing miliary or meningeal tuberculosis and must keep constantly on the watch for signs of these complications.

Five children having severe primary tuberculosis and ranging in age from two to six months were treated with streptomycin. Some received as high as 250 mg. per kilogram per day. Only one of the five has a completely normal response to the caloric test but all have normal hearing. Three have gone home and they seemed well compensated at the time. One of the two children still in the sanatorium is well compensated but the other who was the one receiving 250 mg. per kilogram is now 14 months of age, will undoubtedly have some difficulty when he starts to walk. With our present dosage we might well have prevented this vestibular damage and still have had the tuberculosis run a favorable course.
Primary with Bronchial Complications (PBC)

Nearly 20 per cent of children admitted to Maybury Sanatorium present the dense, homogeneous, lobular, or lobar shadow of the so-called epituberculosis. This x-ray appearance is due to the combination of a large, active, primary, parenchymal focus, tuberculous, peri-bronchial lymph nodes, and some bronchial interference to pulmonary aeration and drainage. Post-mortem examinations of some of these children, dying of miliary and meningeal tuberculosis, demonstrated the bronchial factor as did bronchoscopic examination in many cases.6

In 1941 an analysis was made at Maybury Sanatorium of 42 of these children6 who were examined bronchoscopically. Thirty-one, or 74 per cent, were found to have involvement of the bronchi in one or more of the following forms: extrinsic pressure from enlarged lymph nodes, tuberculoma, ulceration, edema, and redness. Decreased ciliary action in the abnormal bronchus and weak expulsive power in the poorly aerated lung distally may allow the secretions to become inspissated and to act as a plug. In five cases a caseous lymph node draining through a bronchial sinus was observed. Sputum (gastric cultures) of 30 children contained tubercle bacilli and usually this persisted over many months. Forty-one had a positive tuberculin test (one not tested). All showed enlargement of the hilar lymph nodes by x-ray. Thirty-five per cent had the left lung and 65 per cent the right lung involved; the left upper and the right upper and middle lobe were most often involved. The involved lobe was of normal size in 45 per cent, smaller than normal in 50 per cent, and larger than normal in five per cent of the cases. Other than wheezing, most children presented almost no protracted symptoms during the long course of x-ray clearing unless marked progression of the parenchymal lesion, and/or extension by bronchial, lymphatic, or hematogenous routes occurred. Twenty-eight per cent of these 42 children were dead at the end of a ten-year period.

Even children in this group who had a relatively uneventful course were found to have more residual damage than had been suspected by the eventual clearing of the x-ray. In 1945, a bronchographic study was made of 34 children having the above mentioned x-ray, clinical, and bronchoscopic history.7 Bronchiectasis was demonstrated in 24, or 70 per cent of them. It was confined to the lobule, or lobe, which was the site of the previously observed primary disease, and extended from the hilum to the periphery. Twenty-two of these children with only lobular involvement had presented no obvious symptoms of bronchiectasis while one with involvement of the entire middle lobe and the antero-
lateral segment of the right upper lobe had experienced only occasional bouts of fever and cough but had rales over the affected area most of the time. The other child with involvement of the entire right lung had repeated severe attacks of pneumonitis.

Because of the tendency of these lesions to spread, the high percentage of deaths, and the incidence of bronchiectasis in the affected areas it was desirable to investigate the use of streptomycin in the early treatment of this type of case. In August 1947, the American Trudeau Society provided streptomycin for this purpose. Nineteen children were placed in this research group. All had the typical x-ray findings of large hilar lymph nodes and lobar, or lobular, consolidation; 14 had positive sputum cultures at the beginning of streptomycin. In 17 bronchoscopic examination was done; 11 were found to have narrowing of the bronchial lumen and six only excessive secretions. The mean dosage formula used in these cases was as follows: 30 mg. streptomycin per kilogram body weight per day given in three equal injections daily for a period of three months. Table I shows the comparison of these 19 Trudeau-Streptomycin-treated children with 26 similar cases admitted to Maybury Sanatorium during the year 1941.

The results seemed good enough that 16 subsequent children

| TABLE 1 |
| EVALUATION OF STREPTOMYCIN IN PRIMARY TUBERCULOSIS WITH BRONCHIAL COMPLICATION |

| A. Control Series: 101 children admitted to Maybury 1941 (12 mo.) plus 6 year follow-up. | B. Streptomycin Series: 164 children in Maybury 8-1-47 to 2-13-48 (6½ mo.) plus 13½ mo. follow-up. Average and mean dose, 30 mg/kilo/day for three months. |

| No. with typical x-ray | 26 | 19 |
| No. bronchoscoped | 15 | 17 |
| 1. Redness and secretions only | 3 (20%) | 6 (35%) |
| 2. Encroachment on lumen visible | 12 (75%) | 11 (65%) |

Parenchymal clearing of more than 50%:
1. in three months | 7 (29%) | 8 (42%) |
2. in six months | 11 (48%) | 12 (63%) |
3. in 20 months from beginning of series | 16 (62%) | 17 (90%) |

Status 20 months from beginning of series:
1. dead | 4 (15%) | 0 (0%) |
2. at home; doing well | 6 (23%) | 13 (68%) |
3. in sanatorium; condition good | 15 (58%) | 6 (32%) |
4. in sanatorium; progress poor | 1 (4%) | 0 (0%) |

Number Bronchograms
- Bronchiectasis | 7 (71%) | 1 (50%) |
with this type of lesion were given streptomycin after the research project was completed in February 1948. The dosage formula in these 16 is more nearly that in use at the present time, namely 15 to 33 mg. per kilogram (7 to 15 mg. per pound) body weight per day daily for four to seven days, then 15 to 22 mg. per kilogram (7 to 10 mg. per pound) per day three times a week for a total of 42 days over a period of about three months.

All of these 35 children are alive; 27 of them have gone home and the remaining eight are asymptomatic and making satisfactory progress. None has become deaf and only one has vestibular damage. This child was five months old, had an associated questionable miliary tuberculosis and received 41 mg. per kilogram per day for 61 days. Two children had occasional circumoral paresthesia and two transient joint stiffness.

Our impression of these 35 streptomycin treated children in comparison with the 26 admitted in 1941 may be summed up as follows: 1) the rate of clearing of the parenchymal lesions was bettered by 15 per cent in three months and by 30 per cent in 20 months, 2) the rate of recession of the tracheobronchial lymph nodes was not influenced appreciably, 3) spread to other parts of the lung or body was eliminated, 4) the mortality rate was reduced to zero during this 23 months period, 5) the incidence of bronchiectasis may be reduced but a longer follow-up will be necessary to demonstrate the incidence, 6) streptomycin in our present dosage formula is not likely to cause vestibular damage or to preclude a therapeutic response to a second course should it be needed later, 7) sputum conversion occurred more promptly with streptomycin, 8) endobronchial lesions cleared much more rapidly with streptomycin but the effect on narrowing due to pressure of enlarged tracheobronchial lymph nodes was not remarkable.

Reinfection Type Tuberculosis

Four to eight per cent of the children admitted to Maybury Sanatorium have pulmonary lesions which are classified as reinfection type tuberculosis; i.e., there are no active tuberculous nodes at the hila and deposits of calcium are often found. In other instances the child had a known positive tuberculin reaction with a simple primary lesion shown by x-ray a year or so previously. These differ from the extended and complicated primary lesions in which the pulmonary infiltrations are associated with definite hilar adenopathy and are a part of the original process. A differentiation is essential because the method of treatment usually applied in reinfection cases is contraindicated in all primary cases. The x-ray findings in the child with reinfection tuberculosis are almost identical with those in the adult, with cavitation
quite a prominent feature. The symptom picture is also similar. They tend to progress badly without active therapy. Streptomycin in these cases must be used in conjunction with collapse therapy or surgery as part of a carefully planned course of treatment. One must be certain that the streptomycin effect is being sought at the proper time with reference to the success of the collapse because resistant strains of tubercle bacilli emerge in these cases as readily as they do in adults, after which further streptomycin therapy is useless. In the event the patient is a six-year old child with a large cavity one must evaluate the chances of closing that cavity successfully with phrenic paralysis, pneumothorax, pneumoperitoneum, or resection of the diseased lobe or lung, or of temporizing with one or more of those collapse procedures until the patient reaches the age at which permanent collapse by thoracoplasty might be considered, i.e., 16 to 18 years depending on the completeness of bone maturity demonstrated by x-ray.

A few of the lesions encountered in children are such that phrenic paralysis or pneumoperitoneum will suffice but in the advanced cases more extensive collapse or surgery must be used. Pneumothorax has a fairly good possibility of controlling lesions of moderate extent with small cavities; but when the lesions are extensive or the cavities large there is a definite limitation on the effectiveness of this type of collapse. Another limitation is the improbability of pneumothorax providing successful control of the lesion through the critical adolescent period up to thoracoplasty age. In a six-year old child we try first to control the lesion without pneumothorax since even a five-year course of pneumothorax at this time would have burned this bridge when it might be more desperately needed between 11 and 16 years.

Because prolonged treatment must be anticipated in many of these cases the possibility of needing more than the usual course of streptomycin treatment must always be considered. In preparation for a resection the streptomycin should be given intensively for a week before the operation and six to 10 days afterward; i.e., 22 to 66 mg. per kilogram per day in one to three divided doses. In other cases the streptomycin formula is 15 to 33 mg. per kilogram body weight per day, daily for four to seven days and then 15 to 22 mg. per kilogram per day three times a week to a total of 42 doses over a three months period.

Five children, five to 11 years of age, among the 101 streptomycin treated children had collapse measures or pulmonary resection. Two had left pneumonectomy; they became asymptomatic, negative on gastric culture, and have gone home. Both had been in the sanatorium for some time before streptomycin became available and had a shrunken lung, extensive bronchiectasis, and
consistently positive sputum. They received the drug only at the time of operation: 27 and 33 mg. per kilogram per day for less than two weeks. The other three children were treated with collapse measures and two courses of streptomycin. One who had soft non-cavitative bilateral lesions cleared satisfactorily and became negative on gastric cultures with the first course. Had collapse therapy been used at that time relapse probably would not have occurred. However, the disease did reactivate and now with his second course of streptomycin he is receiving pneumoperitoneum and para-aminosaliclyc acid (PAS).

A five year old girl was admitted with two large cavities near the chest wall on the left. With streptomycin the cavities became smaller and left phrenic paralysis was performed during the first course. Serial x-rays have continued to show steady improvement. Five and one-half months after admission she was given another course of streptomycin and pneumoperitoneum was added. She has had a recrush of the left phrenic nerve. For almost a year the cavities have not been seen by x-ray and except for one time the gastric cultures have been negative for tubercle bacilli. Bed rest (modified by the child) is still in effect. Equilibrium and hearing are normal. The fifth case was a small, seven-year old child who had soft exudative lesions throughout both lungs and a 5 cm. cavity with a fluid level in the right antero-lateral segment. With streptomycin the cavity immediately became smaller and right phrenic paralysis and then pneumoperitoneum were added with the result that three months after admission the cavity was invisible by x-ray but gastric cultures did not convert. Three months later coincident with the earliest return of right phrenic nerve function and while the hemi-diaphragm was still markedly elevated the cavity reopened. The second course of streptomycin was started and right pneumothorax attempted. This was abandoned because of adhesions and she was then transferred to the surgical unit for resection.

Nine consecutive reinfection cases were treated in the 1941 series before streptomycin was available with four deaths and five recoveries.

The final results of streptomycin therapy are not yet known but it is expected that at least part of the good early results may be continued so that a greater proportion of these unfortunate children may recover.

Extrapulmonary Tuberculosis

In the extrapulmonary group there are included 13 bone and joint, two lymph adenitis with sinus, one kidney, two pleuritis, one pericarditis, and two peritonitis cases.
The bone and joint cases were given the usual immobilization treatment with surgery as indicated. Streptomycin therapy was not so intensive as in some of the other groups but was continued for longer periods because the bone response is slow. The early cases were treated with the following dosage formula: 15 to 33 mg. per kilogram body weight per day for 42 days, given in one or more daily injections. At present the formula is 15 to 33 mg. per kilogram per day daily for four to seven days then three times a week to a total of 42 doses over a period of three months in the mild cases with no bone destruction and in cases which show prompt disappearance of signs and symptoms. In destructive bone lesions it is given three times a week for 84 doses over a period of about six months. All accessible accumulations of pus are evacuated and when possible, as in the case of a tuberculous rib, the diseased tissue is excised. In cases of empyema 22 mg. per kilogram of body weight is instilled intrapleurally after each aspiration; under intramuscular streptomycin therapy decortication may be carried out. At the time of operation for any extrapulmonary condition 33 mg. of streptomycin per kilogram of body weight is left in the site of operation.

All of these children are alive and all show definite improvement in the lesions. Eight of the 21 children have gone home and the ones in the sanatorium are in good condition. Five had surgery as follows: one fusion of the spine and removal of a portion of tuberculous rib, one fusion of the hip, one decortication for empyema, one nephrectomy, and one pericardial resection. Other bone and joint cases are continuing on immobilization until they are old enough for fusion. Four children had two courses of streptomycin with good results each time.

Because this is a small series it has not been possible to compare streptomycin treated cases with parallel cases treated without it but several observations have been made: 1) general and local improvement is more prompt; 2) there is a decreased tendency to abscess formation and abscesses already present seem to disappear more readily; 3) the bone changes reach the regenerative stage earlier; 4) streptomycin must not be considered as a substitute for any recognized form of therapy but merely as an adjunct to it; 5) the long term results are not yet known.

Discussion

Streptomycin has a rather wide range of use in treating tuberculosis in children. It is mandatory in the treatment of meningitis and miliary tuberculosis. Its next most important use is in the early treatment of tuberculous spreads. Diligence in the detection of new lesions at the earliest possible time cannot be overemph-
asized. It is indicated in acute pulmonary lesions except in simple primary cases and is used effectively in most extrapulmonary tuberculosis. It has a place in the pre- and post-surgical programs. The effect from its use at Maybury Sanatorium has generally been good as shown in Table 2.

The death rate at Maybury Sanatorium has been reduced from 9.8 per cent for a six-year period and 15 per cent for a 26-month period without streptomycin to one per cent for the first 26-month period during which we have had streptomycin. The deaths in meningeal tuberculosis were reduced from 100 per cent to 11 per cent in this same period. This reduction in mortality is no doubt due to the fact that treatment was started early and would have been less dramatic had it been used in the more progressed type of case. Deaths in miliary tuberculosis were reduced from 74 per cent for a six-year period and 88 per cent for a 26-month period without streptomycin to 6 per cent for the 26-month period with

| TABLE 2 |
| MORTALITY IN SANATORIUM CHILDREN |
| *Prior to Streptomycin* |
| Six Years: 1-1-41 to 12-31-46 |
| Follow-up to 3-1-47 |
| | Number | Death | Per cent |
| All Cases | 780 | 77 | 9.8 |
| Miliary | 26 | 13 | 50 |
| Miliary-meningitis | 24 | 24 | 100 |
| Meningitis | 15 | 15 | 100 |
| 24 Months: Comparison Period, 3-44 to 3-46 |
| Follow-up (2 months) to 3-31-49 |
| All Cases | 200 | 30 | 15 |
| Miliary | 10 | 8 | 80 |
| Miliary-meningitis | 7 | 7 | 100 |
| Meningitis | 3 | 3 | 100 |
| *During Streptomycin* |
| 21 Months: 4-22-47 to 1-31-49 |
| Follow-up (3½ months) to 6-16-49 |
| All Cases | 281 | 2 | 0.7 |
| 101 Streptomycin Treated Cases |
| Miliary | 12 | 0 | 0 |
| Miliary-meningitis | 4 | 1 | 25 |
| Meningitis | 5 | 0 | 0 |
| Other Cases | 80 | 0 | 0 |
streptomycin. The fact that only one death has yet occurred among the streptomycin treated children is interpreted as meaning that life has been preserved but not necessarily that death has been prevented; it may occur later as the result of tuberculosis. Streptomycin does not prevent the development of new tuberculous lesions or spreads nor does it give complete assurance against the reactivation of already treated lesions. Evidence has recently been presented to show that the addition of promizole to streptomycin therapy will prevent the development of meningitis in miliary tuberculosis cases, will reduce the incidence of neurological sequelae and will reduce the proportion of relapses. Streptomycin becomes less potent in proportion to the age of the lesions and is almost ineffective against caseous lesions. It cannot compensate for the lack of other good treatment but merely supplements it. The adequate drainage of all abscess pockets is necessary to a good streptomycin effect. Streptomycin is a toxic substance and must be used cautiously. Children tend to tolerate large doses of streptomycin relatively better than adults but they do demonstrate acute toxic and neurotoxic manifestations. When streptomycin is to be used as a life saving treatment it must be given in whatever dosage is necessary despite the risks of loss of equilibrium. In other cases the dosage should be held below 35 mg. per kilogram body weight per day. Children do learn to compensate for the loss of equilibrium but it is not reasonable to subject them to this disability if safe dosage will provide a suitable therapeutic result.

TABLE 3
TOXIC REACTIONS AMONG 101 CHILDREN RECEIVING STREPTOMYCIN

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Hearing Lost</th>
<th>Caloric Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>9</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Predominantly pulmonary (exclusive of PBC)</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Miliary</td>
<td>12</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>2. ? miliary</td>
<td>6</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>3. Babies 2-6 months</td>
<td>5</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>4. Others</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Primary with bronchial complication (PBC)</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Trudeau series</td>
<td>19</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2. Others</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Predominantly extrapulmonary (exclusive of meningitis)</td>
<td>21</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Intensive therapy for longer than 28 days carries the possibility of streptomycin resistant tubercle bacilli emerging and curtailing further therapeutic value of the drug. For this reason initial periods of intensive treatment must be well limited except in those cases in which the clinical effect is delayed and prolonged high dosage is indicated.

The dosage formula given for each group of cases reported is the result of modifying the various early dosage schedules and arriving at one which experience had shown to be suitable. These formulae may be changed in the future based upon further observations but at the present they are the ones being used at Maybury Sanatorium. They are therapeutically sound and are recommended for use by others in treating cases similar to those reported above. Dihydro-streptomycin is reportedly less toxic than the earlier preparations used in this study and may permit the use of more intensive therapy without the hazards of toxic manifestations. The emergence of resistant organisms is apparently as likely with dihydro-streptomycin as with the regular variety. Combined treatment with other chemotherapeutic agents may also modify the dosage schedules and the results. The results of streptomycin therapy have ranged from dramatic recoveries from tuberculous meningitis to disappointing failures in caseating glands but generally they were good. Many children are alive and well because they were treated with streptomycin, many others are recovering. It is anticipated that further good results will be recorded in the future.

Comment

From April 1947 through January 1949, 101 children at Maybury Sanatorium were treated with streptomycin and the results compared with a similar series treated previously in an identical manner without streptomycin. The 101 children included miliary and meningeal cases, severe primary, primary with bronchial complications, reinfection and extrapulmonary cases. The miliary and meningitis cases were given intensive streptomycin therapy at the earliest possible time after the onset of symptoms. The formula for intramuscular therapy was 55 to 88 mg. per kilogram of body weight per day for three to six months depending upon the effect and then 25 to 44 mg. per kilogram per day for the balance of six months. The daily amount was divided into two or three doses according to the size of the child. The meningitis cases were also given intrathecal streptomycin according to the following formula: 2.5 mg. per kilogram, up to 50 mg. maximum, daily for three weeks, then the same dose three times per week for three months and then one-half that dose twice weekly for the balance of six months.
The same courses were repeated in case of relapse. Eighteen cases of miliary tuberculosis, nine of meningitis, and four of miliary-meningitis were so treated. All miliary and meningitis cases and three of the miliary-meningitis cases survived and were apparently recovered at the end of the survey, May 1, 1949. One miliary-meningitis case expired in relapse after making satisfactory early improvement. All had vestibular damage, all compensated well, one is deaf. In the previously treated comparison series, 100 per cent meningitis and 80 per cent miliary cases had died.

Streptomycin was given to five babies with severe primary tuberculosis using the formula of 33 to 66 mg. per kilogram body weight for four to seven days and then one-half that dose three times per week for the balance of 42 doses with satisfactory results. Three recovered completely and two were still making good progress in the sanatorium at the end of the study period.

Nearly 20 per cent of the children admitted to the sanatorium were of the primary with bronchial complication type (extensive epituberculosis). In the previously treated comparison series, 15 per cent had died in the two-year and 28 per cent in a ten-year follow-up study. Bronchial obstruction of various types was found in 74 per cent of the cases. Seventy per cent of them were later found to have bronchiectasis in the involved area. Thirty-five children with this type of tuberculosis were given streptomycin using the following formula: 15 to 33 mg. per kilogram daily for four to seven days, then 15 to 22 mg. per kilogram three times a week for a total of 42 doses over a period of about three months. All 35 children survived and apparently recovered. None suffered any demonstrable vestibular damage. In comparison with the series treated in 1941, the results were as follows: the rate of resolution in the parenchymal lesions were bettered by 15 per cent in three months and by 30 per cent in 20 months, the rate of recession in the tracheo-bronchial nodes was not appreciably changed, spreads to other parts of body, prevalent in the comparison series, was eliminated completely, the mortality was reduced to zero over a 23-month study period and it is anticipated that future studies will show a marked reduction in the incidence of bronchiectasis. Sputum conversions occurred more promptly and endobronchial lesions cleared much more rapidly.

About six per cent of the children admitted by Maybury Sanatorium have reinfection type pulmonary tuberculosis. Five such cases, ranging in age from five to eleven years were included in the 101 cases treated with streptomycin. Besides streptomycin using the same formula as above these children were given collapse or surgical therapy. All five children have survived and all but one give promise of recovery. In the 1941 series four out of
nine children expired within two years. In the extrapulmonary group were included 13 bone and joint, two adenitis with sinus, two pleuritis, two peritonitis, one pericarditis, and one renal tuberculosis cases. In addition to streptomycin each child received all other indicated therapy. The streptomycin dosage formula was 15 to 33 mg. kilogram daily for four to seven days and then three days per week for a total of 42 or 84 dose-days depending upon the response. In the empyema cases, 22 mg. per kilogram were instilled into the pleural space following aspirations. All 21 children survived and made better than previously observed progress.

The overall results of streptomycin therapy in 101 children, observed over a period of 23 months was good. The death rate was reduced from 15 per cent for a comparable 26 month period to 1 per cent. Only one death occurred in the 101 cases treated. A good chance of recovery is given every child with tuberculosis, even miliary and meningitis cases if adequate treatment can be started early and continued for six months or more.

SUMMARY

The results of treating 101 cases of tuberculosis in children with streptomycin in comparison with previously treated cases is reported. The treatment programs used in five different types of cases are outlined including the recommended streptomycin dosage formulae. The results of therapy in each group of cases is recorded with comparative death rates. The unfavorable effects of streptomycin and the precautionary methods are discussed as well as therapeutic limitations.

RESUMEN

Se refieren los resultados del tratamiento de 101 niños con tuberculosis por medio de la estreptomicina, en comparación con casos tratados anteriormente. Los planes de tratamiento usados en cinco tipos de casos diferentes se describen, incluyendo las dosificaciones de estreptomicina recomendadas.

Los resultados del tratamiento en cada grupo son presentados con los coeficientes de mortalidad comparativamente.

También se presentan los resultados desfavorables y se discuten las precauciones así como las limitaciones terapéuticas.

REFERENCES


