The Rehabilitation of Chronic, Drug Resistant Cases of Tuberculosis with Cycloserine, and Successful Treatment of Virgin Cases*

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Cycloserine (CS) was introduced as an antituberculosis drug about five years ago. Since its introduction, we have used it alone or in combination with other agents in the treatment of over 450 cases of pulmonary and other types of tuberculosis at Metropolitan Hospital in New York City. We found its effectiveness against tuberculosis which had become resistant to other drugs most encouraging, and feel that CS has been instrumental in salvaging many of our hopeless cases.

The published material on CS is much too voluminous to mention here. Suffice it to say that in addition to our own work with the drug, various phases of which have been published from time to time, many others throughout the United States, and indeed throughout the world, have used CS as an antituberculosis agent, with a good degree of success.

Besides being an antituberculosis drug, CS is also an effective broad-spectrum antibiotic. Lillic, et al. found it effective in the treatment of various systemic infections due to nonspecific organisms susceptible to it. Cycloserine is highly water soluble and has been found in all the secretions and tissues in which it has been sought, including spinal and amniotic fluid, mother's milk, placental and fetal blood of parturient patients, and in the sputum of tuberculosis subjects. It is excreted into the urine in high concentrations, thus becoming effective treatment in genito-urinary infections due to CS-susceptible organisms. It is effective in donovanosis, but impotent against gonococcal infections, and lymphogranuloma venereum.

The data reported herein were obtained on 397 patients (296 men and 101 women) ranging in age from 13 to 84 years. All were treated for a minimum of six weeks, and 175 were treated for one year or longer. At the start of CS therapy, more than half of the patients had caseopneumonic tuberculosis of relatively recent origin. There were three cases of miliary tuberculosis.

The patients were assigned to certain groups, depending on their clinical status and type of therapy (Table 1), and studied as part of a continuing research project. Other subjects were treated in the wards or outpatient department of the hospital on a routine basis when CS became available commercially, but these are not included in this report.

Prior to CS administration, and in addition to the studies incident to the tuberculous process, all patients were subjected to complete blood studies, liver and kidney function tests, urinalysis, and detailed x-ray film study of the anatomic condition of the lungs. Sputum volume was

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measured and a Gaffky count of tubercle bacilli estimated. The bacilli were cultured periodically and their sensitivity to INH, PAS, streptomycin, and CS was determined according to the methods recommended by the National Tuberculosis Association. Plasma level determinations were made on all but eight of the subjects who are included in this report. Occasionally, the presence of CS was determined in the sputum and urine, as well as in other body fluids.¹⁰

It has been ascertained that CS plasma levels after oral dosing cannot be predicted, but must be determined by chemical assay.¹⁰ We have shown that on the basis of individual patients, the plasma level is closely related to the dose when it is based on the body weight. That is, a doubling of the CS dose in mg./Kg. will about double the plasma level in mcg./ml.¹¹

In a group of 17 subjects in whom the oral dose of CS was from 8 to 22 mg./Kg., the plasma levels ranged from a low of 7 to a high of 48 mcg./ml. It was our observation that most subjects who had plasma levels of 20 mcg./ml. or less did not respond as satisfactorily to the antimicrobial effects of CS as those with consistently higher levels.

It was also demonstrated that the CS plasma level could be used as an index of impending neurotoxicity.¹⁰ This supported our contention that administration of the total daily dose of CS should be made in divided doses.¹⁰,¹⁰ Keeping the unit dose as small as possible virtually eliminated the excessive daily peaks of plasma levels, which were associated with the appearance of toxic reactions. In our experience, a CS plasma level of 30 to 50 mcg./ml. was the "ideal" therapeutic range.¹⁰,¹³ Toxic reactions were most frequent in cases with plasma levels exceeding 50 mcg./ml.; they were rarely seen in patients whose levels were below this.

In addition, we found that pyridoxine administered during CS therapy prevented the more severe neurotoxic reactions and reduced the incidence of tremors and lesser toxic manifestations.¹⁰,¹⁴ Therefore, the concomitant administration of pyridoxine in stubborn or regressive cases allows an increase in CS dosage, with a minimum risk of toxic reactions.

_Treatment of Drug Resistant Cases_

Proof that CS was effective in the treatment of tuberculous infections in man and that tubercle bacilli which had become resistant to INH, PAS, and streptomycin retained their sensitivity to CS afforded new means for the successful treatment of the increasing number of resistant

<table>
<thead>
<tr>
<th>TABLE 1—CYCLOSERINE THERAPY: SUMMARY OF ALL SUBJECTS</th>
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<tbody>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>CS Alone</td>
</tr>
<tr>
<td>CS Alone</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>CS-INH</td>
</tr>
<tr>
<td>CS-INH</td>
</tr>
<tr>
<td>CS-INH</td>
</tr>
<tr>
<td>CS-INH</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Grand Total</td>
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</tbody>
</table>
infections accumulating in our hospital. A first report on 29 such “hopeless,” far-advanced, cavitary cases was made in 1955. Since then, we have treated a total of 139 subjects with drug-resistant infection, 114 with CS alone, and 25 with a combination of CS and INH.

All the patients covered in this study had been on our wards for many years and were doomed to remain there. Their x-ray films showed far-advanced, fibrotic, and destructive lesions which had not changed much under previous therapy. Since fibrotic and cavity-ridden lungs cannot be reconstituted, x-ray films could not be used as a criterion for the effectiveness of CS treatment. We felt that any type of improvement in their clinical picture, such as a lowering in the infectivity of the sputum or a lessening in the degree of cough, would be a change for the better in these subjects.

Data on 106 retreatment subjects who received CS alone are summarized in Table 2. Within two months, 15 patients who had been bedridden prior to the start of CS therapy became ambulatory. All had gained in weight, ate better, were consistently afebrile, and had a brighter outlook on things in general. Within six months after the start of CS therapy, 27 patients left the hospital, often against our advice, because they felt better. In 56 subjects who were treated for at least one year, there was sputum conversion in 22, who were rehabilitated sufficiently to leave the hospital and to be employed gainfully. The poor x-ray film showing of many of these cases re-emphasizes the fact that fibrotic and cavity-ridden lungs cannot be reconstituted.

Table 2 also shows data on 27 subjects who had received 2.0 Gm. of CS daily, with 300 mg. of pyridoxine hydrochloride, as a special project for the demonstration of the protective action of pyridoxine on the toxic effects of CS. Although the number of subjects is relatively small, we believe that the larger dose of CS resulted in a greater improvement in a shorter time. The low incidence of toxicity as related to the plasma levels of these 27 subjects has been reported elsewhere.

Cycloserine combined with INH was given to 25 subjects with drug-resistant tuberculosis. They had been receiving INH and PAS for many months with no sign of clinical or objective improvement. The INH therapy was retained because some patients regressed when the drug

<table>
<thead>
<tr>
<th>CS Dose Gm./Day</th>
<th>Age</th>
<th>Sex</th>
<th>Pre-therapy Status</th>
<th>Sputum Neg. Months</th>
<th>During Therapy</th>
<th>X-ray Impr. Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>F</td>
<td>MA</td>
<td>FA</td>
<td>6</td>
</tr>
<tr>
<td>1.0-1.5</td>
<td>48</td>
<td>62</td>
<td>17</td>
<td>9</td>
<td>70</td>
<td>21/63</td>
</tr>
<tr>
<td>(24-77)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>46</td>
<td>23</td>
<td>4</td>
<td>2</td>
<td>25</td>
<td>10/16</td>
</tr>
<tr>
<td>(23-61)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>47</td>
<td>85</td>
<td>21</td>
<td>11</td>
<td>95</td>
<td>31/79</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Combined Percentile Improvement</td>
</tr>
</tbody>
</table>

*MA = Moderately advanced; FA = Far advanced.
†Fractions indicate total number in the denominator and improved subjects in the numerator.
was removed, and we believed that the INH was exerting a delaying action on the growth of the tubercle bacilli, despite the fact that the patients were resistant to the drug. The results with 1.0 Gm. of CS and 0.3 or 0.6 Gm. of INH daily do not differ in any way from those shown in Table 2, where 1.0 to 1.5 Gm. of CS alone was administered. Similar results have been obtained by others using CS in drug resistant, "salvage" cases.  

Treatment of Virgin Cases

Treatment of virgin cases of pulmonary tuberculosis with CS included 44 subjects who received from 0.5 to 2.0 Gm. of CS daily as the only form of treatment, and 214 who received CS in combination with INH, as shown in Table 1.

Laboratory data had revealed an additive and possibly synergistic effect between CS and INH. This suggested to us that CS could be combined with INH in the treatment of virgin cases. We felt that the combination of CS and INH might destroy the tubercle bacilli before resistance to INH could develop. Even if resistance to INH did develop, CS would continue to be effective because resistance to CS, when it is seen, develops slowly and to a slight degree.

Prior to the start of CS therapy, examination of the patients showed the majority to have cough, fever, a history of weight loss, and profuse sputum which was strongly positive for tubercle bacilli. X-ray films revealed cavitation in the lungs of more than two-thirds of these 258 patients. Table 3 shows the degree of change in the lungs as estimated from the x-ray films. Of the 75 subjects who were treated for a full year, 71, or 95 per cent, showed marked to moderate improvement. Sputum conversion followed a course parallel with the clinical improvement and the x-ray film estimate of the pulmonary involvement.

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**TABLE 3—CS-INH THERAPY: 214 VIRGIN CASES**

**CHRONOLOGICAL CHANGES IN X-RAY FILMS**

<table>
<thead>
<tr>
<th>Degree of Change</th>
<th>Months of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Marked Improvement</td>
<td>3</td>
</tr>
<tr>
<td>Moderate Improvement</td>
<td>85</td>
</tr>
<tr>
<td>Slight to None</td>
<td>121</td>
</tr>
<tr>
<td>Worse</td>
<td>5</td>
</tr>
<tr>
<td>TOTAL</td>
<td>214</td>
</tr>
</tbody>
</table>

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**TABLE 4—CS-INH THERAPY: 191 VIRGIN CASES**

**CHRONOLOGICAL CHANGES IN SPITUM INFECTIVITY**

<table>
<thead>
<tr>
<th>Status of Sputum*</th>
<th>Months of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Negative</td>
<td>84</td>
</tr>
<tr>
<td>Positive on Smear</td>
<td>86</td>
</tr>
<tr>
<td>Positive on Culture Only</td>
<td>21</td>
</tr>
<tr>
<td>TOTAL</td>
<td>191</td>
</tr>
</tbody>
</table>

*Initially, all sputa were strongly positive on smear and culture.
The data summarized in Table 4 show that after two months of combined therapy, the sputa of only 84 of 191 (44 per cent) subjects tested had become negative to smear and culture for tubercle bacilli. However, at this time the sputa of all patients were reduced in volume, cough had lessened markedly, and the number of estimated bacilli per unit volume of sputum had diminished. After four months of treatment, 114 of 169 sputa, or 67 per cent, had become negative to smear and culture. Of 62 subjects remaining at the end of one year, 34 (56 per cent) were negative, with an additional 14 (23 per cent) positive to culture only. These results compare favorably with those obtained after the use of INH-PAS therapy in similar cases.

Table 5 shows the CS plasma levels obtained using CS-INH therapy. The plasma levels of the 164 subjects who received 0.5 Gm. of CS and 0.3 Gm. of INH daily averaged 12.5 mcg./ml.; those from 36 subjects who received 1.0 Gm. of CS and 0.3 or 0.6 Gm. of INH daily averaged 26.9 mcg./ml. These values are comparable to those seen after the use of CS alone.

The clinical efficacy of CS alone in previously untreated patients with advanced, cavitary tuberculosis is illustrated by the data from a group of 16 subjects. These subjects, ten with far advanced and six with moderately advanced tuberculosis, received increasing doses of CS, starting with 0.5 Gm./day, until the plasma levels were between 30 and 50 mcg./ml., where they were maintained with a daily dose of from 1.0 to 2.0 Gm. given in four divided doses. There resulted a prompt and sustained gain in weight and conversion of the sputum.

After 6 to 12 weeks of treatment, only six of the 16 subjects had sputa positive for tubercle bacilli, three to culture only. In all cases, the sputum volume had been reduced and cough was virtually absent, making it difficult to obtain a sufficient amount for smear and culture. Gastric washings were used in all cases where the sputum was negative. At our hospital, the 74 per cent sputum conversion within 24 weeks of treatment is considered to be as good a result as we have obtained with other drug regimens in equally severe cases.

After 12 weeks of treatment, clinical progress as gauged by x-ray film was classified as slight in one, moderate in nine, and marked in five. One was reported as worsening, despite the fact that his initial, highly positive sputum had become negative to smear and culture of gastric washings, and he had gained 28 lb. in weight, after 24 weeks of CS therapy. His plasma levels averaged 43 mcg./ml. from the 1.0 Gm. per day dose of CS. Ten of the 16 patients had temperatures of from 100 to 104°F. at the onset of treatment, all of which became normal within four to six weeks of therapy.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. Cases</th>
<th>Therapy - Gm./Day CS</th>
<th>INH</th>
<th>CS Plasma Levels Average</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>164</td>
<td>0.5</td>
<td>0.3</td>
<td>12.5</td>
<td>2-35</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>1.0</td>
<td>0.3-0.6</td>
<td>26.9</td>
<td>9-48</td>
</tr>
</tbody>
</table>
SUMMARY
1. Data are presented on 397 cases of tuberculosis treated with cycloserine (CS) alone, or in combination with INH. The original purpose of combining CS and INH was to obtain a CS dose which would enhance the antituberculosis effects of INH, while keeping the toxicity at a minimum.

2. Our data show that the therapeutic efficacy of CS, alone or combined with INH, depends upon the attainment and maintenance of CS plasma levels above 20 mcg./ml.

3. The toxicity of CS has been reduced,
   a) by the concomitant administration of pyridoxine hydrochloride, which also protects against INH in combination therapy;
   b) by spreading the daily dose as widely as possible, and
   c) by insuring that the plasma levels of CS are kept well below 50 mcg./ml.

Under this regimen, very few cases had to be discontinued because of toxicity.

4. Cycloserine alone in doses which maintain the plasma level at about 30 mcg./ml. has been shown to induce prompt clinical and roentgenographic improvement, a gain in weight, and rapid reversal of infectiousness, in a large proportion of both resistant and virgin cases of tuberculosis.

5. Bacillary resistance to CS developed but rarely, and in our experience has never been complete, even after continuous administration over several years.

ACKNOWLEDGMENT: The cycloserine used for this study was supplied by Eli Lilly and Company as Seromycin. The CS-INH combination capsules were also obtained through Eli Lilly.

RESUMEN
1. Se presenta la información sobre 397 casos de tuberculosis tratados con cicloserina (CS) sola o en combinación con INH.

El propósito original para combinar cicloserina y la INH fue obtener una dosis de CS que aumentase los efectos antituberculosos de la isoniacida mientras se conservaba una toxicidad mínima.

2. Nuestros datos muestran que la eficacia terapéutica de la CS sola o combinada con INH depende de que se alcance y mantenga un nivel de CS en el plasma arriba de 20 mcg./ml.

3. La toxicidad de la CS se ha reducido por:
   a) El uso concomitante de clorhidrato de piridoxina que también protege contra la INH en la combinación;
   b) la dispersión de la dosis diaria tanto como sea posible y
   c) asegurándose de que el nivel en el plasma se mantenga bien abajo de 50 mcg./ml.

Bajo este régimen muy pocos casos han requerido la suspensión del tratamiento por la toxicidad. La cicloserina sola en dosis que mantenga el nivel en el plasma alrededor de 30 mcg./ml. ha demostrado que produce mejoría clínica y radiológica, aumento de peso y rápida desaparición de la infecciosidad en gran proporción de casos ya sean resistentes o casos no tratados previamente, de tuberculosis.

5. La resistencia bacilar a la CS se presentó pero rara vez y según nuestra experiencia nunca ha sido completa aún después de interrupción de la administración por varios años.

RESUMÉ
1. L'auteur présente ses conclusions sur 397 cas de tuberculose traités par la cycloserine et l'isoniazide. L'auteur s'était primitivement proposé d'obtenir une dose de cycloserine qui renforcerait les effets antituberculeux de l'isoniazide, tandis qu'elle aurait une toxicité réduite au minimum.

2. Ses constatations montrent que l'efficacité thérapeutique de la cycloserine, seule ou associée à l'isoniazide, dépend du fait qu'on puisse atteindre et maintenir des taux de cycloserine dans le plasma au-dessus de 20 mcg./ml.

3. La toxicité de la cycloserine a été réduite:
   a) par l'administration simultanée d'hydrochloride de pyridoxine, qui protège également contre l'isoniazide dans l'association thérapeutique;
   b) en distribuant la dose quotidienne en autant de prises que possible;
   c) et en s'assurant que les taux dans le plasma de la cycloserine sont bien en-dessous de 50 mcg./ml.

Avec cette posologie on ne doit arrêter le traitement à cause de la toxicité que dans un très petit nombre de cas.

4. La cycloserine seule, à des doses qui maintiennent le taux plasmatique aux environs de 30 mmg./ml. se révèle capable de produire une amélioration rapide clinique et radiologique, un gain de poids, et une sédation rapide de la maladie, dans une grande proportion de cas de tuberculose aussi bien résistants que traités pour la première fois.

5. Une résistance bacillaire à la cycloserine a pu se développer mais de façon rare et dans l'expérience de l'auteur, n'a jamais été totale, même après administration continue pendant plusieurs années.
ZUSAMMENFASSUNG

1. Es wird das Zahlenmaterial vorgelegt von 397 Fällen von Tuberkulosen, die mit Cycloserin (CS) allein oder in Kombination mit INH behandelt wurden. Die ursprüngliche Absicht der Kombination von CS und INH war, zu einer CS-Dosis zu kommen, welche die antituberkulöse Wirkung von INH steigerte und die Toxizität gleichzeitig auf einer niedrigen Höhe hielte.


3. Die Toxizität von CS fiel sich verringern durch:
   a) die gleichzeitige Verabfolgung von Pyridoxin-Hydrochlorid, das auch gegen INH bei der Kombinationstherapie eine Schutzwirkung hat;
   b) die Verteilung der Tagesdosis, soweit wie irgend möglich, auf verschiedene Stunden und
c) die Sicherstellung, daß die CS-Plasma-Werte eindeutig unter 50 Mikrogramm pro Kubikzentimeter bleiben.

Bei einem solchen Vorgehen erfahren sehr wenig Fälle eine Unterbrechung wegen Toxizität.


5. Es kam wohl zu einer basiliären Resistenz gegen CS, aber sehr selten, und sie war auch nach unseren Erfahrungen niemals vollständig, selbst nach über mehrere Jahre fortgesetzter Anwendung.

REFERENCES


PERINATAL DISTRESS SYNDROME

Pulmonary hemorrhage in the newborn may occur in small, clinically insignificant amounts or may at times be massive, resulting in rapid demise. Fetal anoxia is probably the most probable cause, although this may be complicated by hypothermia or hemorrhagic disease of the newborn. Pulmonary hemorrhage frequently accompanies fatal erythroblastosis fetalis. No clinical findings may be limited to respiratory distress or, in the severe cases, there may be hematemesis or the passage of large amounts of foxy blood from the nose and mouth. Radiographs of the chest show linear and patchy areas of increased density, usually in both lungs, and the prominence of the markings and the distribution depend upon the severity of the intra-alveolar hemorrhages.


SPONTANEOUS CLOSURES OF VENTRICULAR SEPTAL DEFECTS

A group of 37 children is described in whom a systolic murmur heard early in life gradually diminished and eventually disappeared. When the patients were first seen, the clinical findings suggested a small ventricular septal defect but no thrill was present and the systolic murmur had a superficial blowing quality with high-frequency vibrations and tended to stop before the second heart sound. Cardiac catheterization demonstrated a small left-to-right shunt at ventricular level in four of the patients while the murmur was present; in one, this was repeated after the murmur had gone and no abnormality could be demonstrated.

Cardiac catheterization in other patients with typical disappearing systolic murmurs showed a left-to-right shunt in some, but in others, this was too small to be detected by routine oxygen studies. With angiocardiography and intracardiac phonocardiography, the exact site of the ventricular septal defect was localized to the muscular portion of the septum in four of the patients.

In one patient who presented with congestive heart failure, clinical and hemodynamic findings of a large ventricular septal defect disappeared. Children with the specific type of systolic murmur described may be recognized as having a small defect in the muscular ventricular septum. The defect is thought to be gradually reduced in size and ultimately closed by hypertrophy of septal muscle. Spontaneous closure appears to be not uncommon with small ventricular septal defects and may occur rarely with lesions large enough to present with congestive heart failure.