The Treatment of Pulmonary Tuberculosis  
with Isonicotinic Acid Hydrazide*

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Application of isonicotinic acid hydrazide and related compounds under  
the name Rimifon, Nicotbine, Tizide, Ditubine, was carried out in a total  
number of 160 cases in the University Clinic of Phthisiology of Athens at  
the Sanatorium "Sotiria".

The present study concerns only 36 cases of pulmonary tuberculosis  
of which four had tuberculous laryngitis.

The limited number of 36 selected cases out of 160 is due to the following  
two important factors, (1) because the duration of the applied therapy is  
from two and one-half to three and one-half months and, (2) because in  
these cases the clinical observation as well as the x-ray and the laboratory  
control were considered as complete.

Most of our patients chosen for this study had far advanced pulmonary  
tuberculosis and uniformly bad prognosis, e.g. progressive, evolutive, bi-

tal cavitary tuberculosis, because such is the condition for the most part  
of patients under treatment at Sotiria.

Besides, we wanted to try the effectiveness of the drug in cases of bad  
prognosis because the first published data in the Quarterly Bulletin of  
Seaview Hospital, Vol. XIII, No. 1, January 1952, reported extremely favor-

able results in such cases.

Here is a summary of the results obtained in these 36 cases:

BEFORE TREATMENT

Sex: all female patients.
Age: From 19 to 25 years .................. 19  
       25 to 40 years ...................... 14  
       40 to 45 years ...................... 3


Duration of Disease Prior to Treatment:

From 6 to 12 months ..................... 3  
       12 to 24 months .................... 7  
       24 to 48 months .................... 5  
       48 to 60 months and over .......... 21

Previous Ineffective Treatment:

1) Hygiene and bed-rest. Duration:

From 4 to 8 months ..................... 8  

Up to 12 months ....................... 5  

24 months ............................ 8  

36 months and over ................... 15

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2) Collapse Therapy:
   a) Artificial Pneumothorax,
      Unilateral ........................................ 19
      Bilateral ........................................ 3
   b) Phrenic crush .................................... 6
   c) Pneumoperitoneum ................................. 2
   d) Cavernostomy .................................... 3
3) Antibiotic Therapy: Streptomycin,
   In 13 cases ......................................... 20 to 100 gm.
   23 cases ........................................... 100 to 200 gm.
4) Chemotherapy:
   a) Para-aminosalicylic acid (PAS),
      In 9 cases ........................................ 500 to 1000 gm.
      27 cases ......................................... 1000 to 3500 gm.
   b) Thiosemicarbazone (Conteben),
      In 8 cases from 1 gm.,
      38 gm. maximum total dosage.
Classification of Cases:
Anatomicopathologically (By Roentgenography)
(By Tomography,
   Extension,
      Unilateral ........................................ 3
      Bilateral ........................................ 33
   Form,
      Exudative ........................................ 4
      Productive ....................................... 8
      Exudative-productive (mixed) ............... 24
   Cavitary,
      Solitary-cavitary ............................... 1
      Unilateral ..................................... 15
      Bilateral ..................................... 20
   Clinically,
      Progressive evolutive .......................... 36
      intensily in 23; slowly in 12.
      Stationary ....................................... 1
Symptomatology - Semiology:
   Cough,
      Slight .......................................... 22
      Intense ......................................... 12
      Excessive Intense ............................... 1
   Expectoration,
      Copious ......................................... 25
      Moderate ....................................... 8
      Scanty .......................................... 3
   Temperature,
      Subfebrile ...................................... 4
      Fever ........................................... 8
      High fever .................................... 24
   Toxicity,
      Intense ......................................... 23
      Moderate ....................................... 10
      Non-existing .................................... 3
Laboratory Findings:
   Sputum examination for tubercle bacilli,
      Positive ....................................... 35
      Negative ....................................... 1
TREATMENT OF TUBERCULOSIS WITH INAH

Erythrocyte sedimentation rate,
- Rapid ........................................... 34
- Moderate ....................................... 2

Urinary findings,
- Hemoglobin slightly positive ................. 1
- 0.20 0/00 of albumin without casts .......... 1
- Traces of albumin ................................ 6
- Urobilin slightly positive ...................... 2

Blood,
- Increase of white cells ....................... 12
  from 9,200 to 19,000.
- Reduced red blood cells ..................... 5
  1st case, 2,560,000; 2nd case, 2,830,000;
  3rd case, 2,860,000; 4th case, 3,130,000;
  5th case, 3,380,000.

Tests of liver function,
  Turbidity test,
    Thymol,
      In 30 cases .................................  
      In 6 cases .................................. +
    Zinc sulfate,
      In 12 cases .................................
      In 24 cases .................................. +

  Flocculation test,
    Thymol,
      In 3 cases .................................
      In 33 cases .................................. +
    Cephalin in all 36 cases ...................... +
    Colloid gold in all 36 cases .................. +

The average daily dosage was 4 mg. per Kg.
  of body weight. In some cases the dosage was
  increased from 5 to 7 mgs.

RESULTS OBTAINED DURING AND AFTER TWO AND ONE-HALF
TO THREE AND ONE-HALF MONTHS' TREATMENT

Cough and Expectoration:
A temporary rise was observed in many cases at
the beginning of the treatment. There was gen-
erally observed,
  Was considerably diminished up to the
    end of the treatment .......................... 14
  Was temporarily diminished .................... 5
  Was moderately reduced ........................ 17

<table>
<thead>
<tr>
<th>Returned to Normal</th>
<th>Considerably Reduced</th>
<th>Slightly Reduced</th>
<th>Stationary</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) In 24 with temperature of 38-40 degrees C.</td>
<td>7</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>b) In 8 with temperature of 37.4-38 degrees C.</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>c) In 4 with temperature of 36.9-37.4 degrees C.</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

In nine cases fever reappeared one and one-half
months after being reduced.

Appetite,
  Remained stationary .......................... 13
  Slightly improved ............................ 8
Among the 15:
   Ravenousness was observed in .............. 3
Among the 15 who improved:
   Appetite remained increased in ............. 14
   Was temporary in ................................ 9
Weight,
   Increased from 1 to 5 Kg. .................... 15
   Increased from 5 to 10 Kg. .................... 4
   Increased up to 20 Kg. ....................... 1
   Stationary ..................................... 13
   Reduced from 1½ to 6 Kg. .................... 3

General condition: concerning toxic symptoms as + weakness, fatigue, sweats, depression,
   All toxic symptoms reduced or completely disappeared in all patients except two. The amelioration of the general condition in four bedridden patients is extremely satisfactory. They got up and started walking easily enough. In nine among the improved ones, the toxic symptoms reappeared one and one-half months later.
Auscultation,
   Considerable decrease in rales and modification of them into dry was observed in two. Relative decrease in rales was observed in 11. The auscultatory examination remained stationary in 20. Deterioration by expansion of rales is observed in three.
   The improvement of the general condition, of appetite and temperature was not parallel with the auscultation findings.

Roentgenographic changes (Roentgenograms and Tomograms),
   Disappearance or resorption of shades existing around cavities or foci as well as reduction in cavity size is observed in nine; remained stationary in 23; and deteriorated in four.

**Laboratory Findings:**

<table>
<thead>
<tr>
<th></th>
<th>Considerably Reduced</th>
<th>Moderately Reduced</th>
<th>Stationary</th>
<th>Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>6</td>
<td>4</td>
<td>20</td>
<td>3</td>
</tr>
</tbody>
</table>

Sputum examination for tubercle bacilli,
   Before treatment the sputum was positive in 35 cases. After treatment the sputum examination was positive in 25, negative in 10 cases.
   Culture followed in the 10 negative cases. Here are the given results: negative, four; positive, six. Single sputum-negative case before treatment remained negative.

Blood,
   Red blood cells: Four among the five with reduced red cells (2,580,000 to 3,380,000) per cemm. before the treatment, presented during and after treatment a steady increase of 1 to 2 millions. The fifth case remained stationary. In three cases the number of red cells is reduced from 1 to 1½ million, though before the treatment the number was normal.
   White blood cells: In 10 among 12 with increased number of leucocytes (over 9,000) before the treatment returned to normal limits, while in two their number remained stationary. Increase of monocytes was observed in six cases. No considerable increase of eosinophils was observed.

Side effects,
   Somnolence in two; vertigo in one; dizziness in one; headache in five (extremely severe in one); disturbance of urination in one; increase of reflexes in four; tachycardia in one; excitement in none; constipation in none.
   The treatment was not discontinued on account of the above-mentioned side-effects, because they were temporary.
Checking of liver function during and after the treatment.

Turbidity Test:
Thymol,
All 30 cases remained steadily negative after treatment. Among the six positive cases four became negative and two remained positive after treatment.
Zinc sulfate,
Twelve remained steadily negative after treatment. Among the 24 positive cases 18 remained positive and eight became negative.

Flocculation Test:
Thymol,
All three negative cases remained negative after treatment. Among the 33 positive cases 23 remained positive and 10 became negative as before.
Cephalin,
Among the 36 positive cases, 30 remained positive and six became negative.
Colloidal, gold,
Among the 36 positive cases, 28 remained positive and eight became negative.

An adequate proportion of cases with positive liver function tests before treatment, later became negative. From this fact we have come to the conclusion that, thanks to the improvement made by the new therapy, the liver rid itself of the toxicity.

On the other hand, the cases with negative liver function tests remained steadily negative after the treatment. Consequently the new drugs do not overcharge the function of liver.

Urine examination: In a single case the protein increased from 0.20 0/00 to 1 Gm.

Relapse:
Nine patients presenting clinical improvement relapsed after one to two months treatment, and all the toxic symptoms reappeared. Among the relapsed cases the focal lesion was deteriorated in one, and remained stationary in eight. There are two possible explanations for the reappearance of the toxic symptoms, (a) that the effectiveness of the therapy was no longer sufficient and b) that the tubercle bacilli acquired resistance to these drugs.

In 1, death occurred on the 46th day of treatment
In 1, death occurred on the 47th day of treatment
In 1, death occurred on the 57th day of treatment
In 1, death occurred on the 96th day of treatment.

SUMMARY
1) Serious toxic reactions have not been seen by the use of these new drugs in a dosage of 4 to 5 mg. per Kg. of body weight.
2) With the administration of these compounds no clinical unfavorable influence was observed.
3) The temperature, the toxic symptoms, as appetite, fatigues, sweats as well as the general condition of the patients were favorably influenced from the first days of treatment.
4) The more elevated the temperature the more favorably it is influenced.
So, within three to six days the temperature fell by crisis to normal limits or remained at a lower degree, while slight fever was hardly influenced.

5) It was impressive how appetite was regained, reaching in certain cases the limits of ravenousness.

6) We have been impressed by the fact that patients of bad prognosis confined permanently to bed on account of their severe toxic condition got out of bed and strolled around the clinic.

7) Intense cough was greatly influenced. The incessant cough of one patient not influenced by the common drugs, gradually diminished and finally disappeared.

8) Expectoration decreased in half of our cases. It is interesting to notice that, the more copious the sputum previously was, the more reduced it became.

9) Unfortunately amelioration in the general condition and symptoms of the patients was not followed by adequate improvement in the auscultatory findings except in two cases.

10) Satisfactory x-ray film modification was not observed. In nine cases it consisted of considerable reduction or complete disappearance of the pericavitary and perifocal shadows. The foci themselves were not influenced. In a few cases only the existing cavities became smaller. In certain cases roentgenograms taken after the treatment showed disappearance of pre-existing cavities. But tomography taken afterwards demonstrated that cavities existed as before.

11) It is interesting to note that in nine cases despite the clinical amelioration after a one and one-half to two months treatment, a relapse occurred and consequently all the toxic symptoms reappeared. In eight of these cases the focal process remained stationary and in one, deteriorated. Consequently, in a certain number of cases, the administration of the new drugs did not manage to stop the further evolution of the disease despite the temporary amelioration: four of these nine patients died. Intense toxic symptoms in certain cases were considerably diminished.

In case of primary infection, the new drugs must be administered with the maximum dosage daily (4-5-7-10 mg. per Kg. body weight) for one to three months, until the morbid symptoms disappear. Afterwards, the administration of streptomycin must follow (three times a week) in a total quantity of 15-20-30-40-50 Gm. while simultaneously PAS is given per os, long after streptomycin is discontinued.

In case of chronic tuberculosis associated with intense toxic symptoms, the hydrazides must be administered in order to reduce or make the toxic symptoms disappear. On the other hand, the administration of the new drugs in cases of chronic tuberculosis without toxic symptoms is useless.

When collapse therapy in certain cases of chronic tuberculosis is indicated, it should not be postponed or replaced by the new drugs. We do not know yet whether the administration of 10 mg. per Kg. of body weight per day instead of 4 to 5 mg. of isonicotinic acid hydrazide might give us better results, especially in focal processes.
RESUMEN

1) No se han visto reacciones tóxicas de seriedad, usando esta nueva droga a las dosis de 4 a 5 miligramos por kilo de peso.

2) No se observó con el uso de las mismas, ninguna influencia clínica desfavorable.

3) La temperatura, los síntomas tóxicos, tales como el apetito disminuido, los sudores y la fatiga, así como el estado general, fueron favorablemente influenciados desde los primeros días del tratamiento.

4) Mientras más elevada es la temperatura, mayor es la influencia favorable. Así, dentro de los tres a seis primeros días, la temperatura descendió por crisis a los límites normales o permaneció en grados menores, en tanto que cuando la fiebre era ligera apenas era modificada.

5) Fue impresionante notar como el apetito se recobró llegando en ciertos casos a ser voraz.

6) Nos impresionó también, el hecho de los enfermos con mal pronóstico confinados de manera permanente en la cama a causa de sus condiciones de severa toxicidad, abandonaron la cama y deambularon por la clínica.

7) La tos intensa fue grandemente influenciada. La tos incesante de un enfermo que no había sido modificada por medio de las drogas comunes, gradualmente disminuyó y finalmente desapareció.

8) La expectoración decreció en la mitad de nuestros casos. Es interesante notar que mientras más copioso era el esputo antes, más se reducía después.

9) Desafortunadamente la mejoría no fue seguida de cambios correlativos a la auscultación, salvo en dos casos.

10) No se observó modificación satisfactoria en las películas de rayos X. En nueve casos consistió en considerable reducción o completa desaparición de las sombras pericavitarias y perifocales. Los focos mismos no fueron modificados. En pocos casos solamente las cavidades roentgenogramas tomados después del tratamiento mostraron completa desaparición de las cavidades pre-existentes.

11) Es interesante notar que en nueve casos a pesar de la mejoría clínica después de uno y uno medio o dos meses, una recaída ocurrió y todos los síntomas tóxicos reaparecieron. En ocho de estos casos, la infiltración focal, permaneció estacionaria y en uno empeoró. En consecuencia, en cierto número de casos la administración de la droga no logró detener la evolución ulterior de la enfermedad a pesar de la mejoría temporal.

RESUME

1) On n’a enregistré aucune réaction toxique avec ces nouvelles drogues à la dose de 4 à 5 mmgr. par kilogramme de poids corporel.

2) Aucune influence clinique défavorable ne fut observée après administration de ces produits.

3) La température, les symptômes toxiques, tels que l’appétit, la fatigue, les sueurs, aussi bien que l’état général du malade, se sont trouvés favorablement influencés depuis les premiers jours du traitement.
4) Plus la température est élevée, plus elle est favorablement influencée. Ainsi, après trois à six jours, la température tombe en crise jusqu'à la normale, ou bien reste à un degré assez bas, tandis que les fièvres légères sont à peine influencées.

5) Il est impressionnant de noter combien l'appétit est stimulé, atteignant dans certains cas les frontières de la boulimie.

6) Nous avons été frappés par le fait que les malades pour lesquels le pronostic était sombre, et qui étaient confinés au lit à cause de la gravité de leur intoxication, ont pu quitter leur lit, et se promener autour de la clinique.

7) La toux fut grandement influencée. C'est ainsi que pour un de nos malades, sa toux incoercible qui n'avait pas été modifiée par les traitements habituels diminua progressivement et finalement disparut.

8) Dans la moitié de nos cas, l'expectoration diminua. Il est intéressant de noter que plus elle était abondante auparavant, plus elle fut réduite ensuite.

9) Malheureusement, l'amélioration ne fut pas corroborée par les signes d'auscultation sauf dans deux cas.


11) Il est intéressant de noter que dans 9 cas, en dépit de l'amélioration clinique après un mois et demi ou deux mois de traitement, une rechute apparut accompagnée de tous les symptômes toxiques. Dans huit de ces cas, le processus resta inchangé, et dans un cas fut remanie. Par contre, dans un certain nombre de cas, l'administration des nouveaux produits ne réussit pas à arrêter l'évolution ultérieure de la maladie, malgré une amélioration momentanée.