The Present Status of Isoniazid in the Treatment of Pulmonary Tuberculosis*

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After the sensational announcement of isoniazid as a remedy for tuberculosis a little over a year ago, it is highly proper at this time to inquire about its present status—to assess its value and to describe its mode of action as much as the known facts will permit. There is no doubt that the first wave of enthusiasm was not entirely justified by subsequent trials in various forms of tuberculosis. It fell considerably short of the ideal chemotherapeutic agent. For example, it is not definitely bacteriocidal and the bacilli soon gain resistance. On the other hand, it has achieved results that are equal to and perhaps superior to streptomycin in certain aspects of treatment of the disease. Combined with other drugs it constitutes a distinct advance in anti-tuberculosis therapy.

There is no point at this late date to go into the historical development of this interesting chemical. The early experiments were reported by several different laboratories and clinics.1–8 As an organic compound it is a relatively simple one. It was first prepared in 1912 and it lay on the chemists shelf for nearly 40 years before its usefulness in tuberculosis was discovered. As an agent against tuberculosis it may be compared to the keystone of the Arch of the Temple that was by-passed for a long period of time before its true place was found.

It must be pointed out that all of the actions and the exact mechanism of the action of this interesting chemical on the tubercle bacillus and on the human body, is by no means completely solved. There seems to be little question that there is a stimulating effect upon the body that is not possessed by any other anti-tuberculosis agent although streptomycin does create some feeling of well being due perhaps to the cutting off of toxins caused by the disease. There seems to be, on the part of isoniazid, a direct cerebral stimulation over and above that on the disease thus causing a feeling of well being and a stimulation of appetite. It may be due to the fact that the niacin fraction of the isoniazid may possess an action on the body over and above that produced by the action on the tubercle bacillus.

The action on the tubercle bacillus itself has been studied by various workers with the result that much has been learned concerning the mech-

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*From the State of Florida Tuberculosis Hospital System.

The Isoniazid for these experiments was furnished by:
1) Pfizer & Co., Brooklyn, N. Y. Courtesy of Dr. Gladys Hobby.
2) Parke-Davis & Co., Detroit, Mich. Courtesy of Dr. C. M. Sharp.

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anism of the action on the tubercle bacillus, both in vitro and in vivo. One of the most interesting and important studies was carried out by Barkley, Ebert and Koch-Weser. The growth curves of tubercle bacilli recorded by these authors in Dubos-Davis Medium revealed the fact that isoniazid was not bacteriocidal. Growth did not stop immediately when the bacilli came in contact with isoniazid but continued on for at least another generation. This indicated to these authors that isoniazid interfered with some vital metabolite rather than causing any abrupt cessation of growth activity. After the drug is added there is enough of the metabolite present in the bacilli to continue on for another cell division before activity stopped. Indeed they suggested that the isoniazid may have entered into the formation of a combination with some vital enzyme and diverted it from its action. This result was different from that obtained with streptomycin where there was an abrupt cessation of growth activity as soon as the bacilli came in contact with the drug. Furthermore, there was a liquefaction of many bacteria exposed to streptomycin showing that there was a considerable bacteriocidal action. This effect was not produced at all by isoniazid.

These same authors developed an ingenious method of testing the effect of isoniazid on the resistant and non-resistant strains of tubercle bacilli. They caused to be made in the chemical laboratory a radio active isoniazid by incorporating “carbon 14” in the carboxyl position of the isoniazid molecule. The experiments revealed that sensitive bacilli took up the compound in large quantities whereas the resistant strains took up practically none.

Steenken and Wolinsky were able to heal experimental lesions in rabbits by intensive isoniazid treatment so that no growth or infections could be produced from the lesions. The explanations could be that the rabbits were infected entirely with bacilli undergoing active cell division.

Of great interest also is the work of Mackaness and Smith on the extracellular and intracellular tubercle bacilli treated by various anti-tuberculosis agents including isoniazid, streptomycin and terramycin. These authors found that isoniazid perhaps due to its small molecule penetrated specially prepared macrophage cells containing tubercle bacilli and prevented growth activity of the bacilli within these cells. This action was almost equal to that obtained by isoniazid in extracellular fluids. Streptomycin did not have intracellular activity except in high concentrations. These observations are most important and perhaps help to explain much of the favorable effect of isoniazid in milliary tuberculosis and tuberculous meningitis where the penetration of cells is important. For the same reason it may be that the smaller molecules of isoniazid will penetrate caseous material, better than streptomycin and will reach more tubercle bacilli buried deeply in caseous lesions. One of the most striking results of isoniazid treatment is in tuberculous meningitis where the saving of lives has been increased from an average around 20 per cent of all forms of meningitis to around 60 per cent, although other factors have entered in, such as earlier diagnosis and better regulated and uninterrupted treatment.
Figure 1: Copy of chest roentgenogram taken July 10, 1952 of E. K., Case No. 2840—a 30 year old colored female before treatment.—Figure 2: Same as Figure 1 on January 31, 1953 after five months and 20 days treatment with INAH alone. Two large annular shadows in the left lung have disappeared from view together with much clearing of other lesions. Sputum is negative.
At present it may be affirmed that there is yet no ideal chemotherapeutic agent against the tubercle bacillus. None of them are directly bacteriocidal. Isoniazid especially is only active against tubercle bacilli that are undergoing metabolic activity and are multiplying by cell division. There are undoubtedly dormant phases of tubercle bacilli that are not touched by isoniazid or even streptomycin. These are the "sleepers" that come out later on and reactivate disease after it was apparently on the way to quiescence and cure.

The most unfavorable feature of the action of isoniazid on tuberculosis is the development of resistance of bacilli against the drug. It is even more marked than that observed against streptomycin. Combining isoniazid with streptomycin does not reduce the development of resistance in bacilli against the isoniazid as much as against streptomycin which does reveal a considerable delay in resistance as a result of the presence of isoniazid. It is even more marked than the reduction in resistance produced by PAS. This feature has been demonstrated by the United States Public Health Service study. In this study isoniazid was better than PAS in preventing bacillary resistance to streptomycin, but the presence of streptomycin reduced the development of resistance to isoniazid only from about 50 per cent to about 20 per cent. The conversion rate of streptomycin and isoniazid was much more than isoniazid alone and more than the combination streptomycin and PAS.

There are many unexplored phases of the action of isoniazid on tubercle bacilli and on the disease tuberculosis, but the combination of isoniazid and streptomycin seems to give the best results of any other combination used up to now. MacKaness and Smith have shown that the combination of INAH and streptomycin has more than a simple additive effect of the two agents. Bacilli are inhibited in concentrations in lower dilutions of each drug in combination than in the drugs when used alone. This observation has been borne out by the United States Public Health Service study. The future may unfold many other useful combinations with such drugs as PAS or with streptomycin and PAS together with INAH. Perhaps there is no greater usefulness of isoniazid than in cases with resistance to streptomycin and or PAS.

It is our pleasure to report on a limited study carried on at the Southwest Florida Tuberculosis Hospital. A brief summary of the work will be given at this time. It consists of two parts—26 cases treated with INAH alone and 10 with INAH and streptomycin.

The indications for isoniazid are little different than those for streptomycin. Without going into all the various types of tuberculosis where it produces best results, let it be said that the acute, infiltrative, and recently formed lesions respond best. Or put in another way, it is best where the drug is most readily accessible to growing tubercle bacilli. It doesn't matter whether the lesions are large or small or have an inflammatory (exudative) or fibroplastic (productive) tendency. The important feature is the accessibility of the drug to rapidly growing tubercle bacilli. Infiltrative, bron-
Figure 3: Copy of roentgenogram of patient P. P. on July 25, 1952. Case No. 2390—a 34 year old colored female before treatment. Figure 4: Same as Figure 3 on March 21, 1953 after seven months and 20 days of treatment with INAH alone. Note the clearing of infiltrations and the shrinking of the cavity in left midfield.
chopneumonia, pneumonic, miliary, and small nodular lesions, therefore, respond best.

On the other hand, old fibrotic types where the bacilli are sluggish in growth or are buried deeply in fibrotic tissue or in caseous masses, the effect is much less or not at all. Heavily encapsulated and partially calcified lesions show little response.

The toxicity of INAH in dosage less than 5 mgs. per kilo, is not serious except in central nervous system disease such as epilepsy, schizophrenia, etc. Outside of these conditions the most common complication, that is annoying, but not critical is an allergic reaction. There were two cases among those being reported where allergy was present, one was fleeting and soon passed off, but the other was serious, producing high fever, nausea, headache, malaise, itching, and marked erythema. Benadryl controlled the most of the unpleasant symptoms. After several attempts to resume treatment, it was found necessary to desensitize the patient by using a small initial dose and adding 1 mg. a day until 200 mgs. a day were tolerated without ill effects.

Selection of Cases:

There were 26 cases in the first group treated with INAH alone for a minimal period of three and one-half months and a maximum period of 10 months. The dose was 150 mgs. per day in patients weighing less than 100 pounds at the beginning of treatment; 200 mgs. per day in those weighing from 100 to 135 pounds; and 250 mgs. per day in those weighing from 135 to 170 pounds; 300 mgs. per day in those above 170 pounds. It is questionable whether more than 5 mgs. per kilo should be given. Barkley, Ebert and Koch-Weser9 claim that large doses do not increase the therapeutic efficiency. Clinical laboratory and x-ray examinations were made monthly. In the laboratory examination the following tests were performed: Red blood count and hemoglobin; sedimentation rate; hematocrit; total protein; albumen; globulin; the A/G ratio; urea nitrogen; and urine examination.

There were 13 white and 13 colored patients; 11 male (eight white and three colored); and 15 female (five white and 10 colored). The stages of the disease were represented by 24 far advanced and two moderately advanced cases.

Results of Treatment:

Perhaps the most outstanding noticeable effect on the patient is the cessation of toxicity with corresponding increase in the feeling of well being, reduction of the temperature and pulse and tremendous increase in appetite and subsequent gain in body weight. Many cases began to show improvement the first week and some within a few days. Generally there was also a marked decrease in cough and expectoration. The cases having large cavities usually had a decrease in sputum in proportion to the extent of overall cavity closure. Some without cavity formation became entirely sputum free as well as bacillus free. Of 26 patients 21 (81.0 per cent)
**Figure 5:** Copy of chest roentgenogram on May 7, 1952 of P. F. Case No. 3005—a 43 year old colored male, after one month of treatment with SM and PAS. **Figure 6:** Same as Figure 3 after four months treatment with SM and PAS. Note the annular shadow has enlarged but infiltrations have largely disappeared.
showed moderate to marked improvement, and all but one showed some improvement.

Weight gain was equally impressive. Of the 26 cases 12 (46.1 per cent) gained 20 pounds or more; five (19.2 per cent) gained from 10 to 20 pounds; and eight (30.6 per cent) gained one to 10 pounds. All but one gained weight.

There is nothing remarkable in the results in sex or race as they all seemed to react similarly.

Radiological changes were slower to appear than some of the clinical changes, yet after several months the changes became striking and in the same order as the clinical changes. The most dramatic change is in cavity shrinkage and closure. Sometimes the cavity will shrink to half or a third of its original size and then enlarge again which may be a result of the development of resistance in the bacilli. One case having surgery, revealed a small stellate cavity about a fifth the original size on pathological examination. The figures for marked improvement are, 11 (42.3 per cent); for moderate improvement, five (19.2 per cent); with two showing no change and three (11.5 per cent) showing deterioration and spread of the lesions. There was no race and sex difference worthy of mention. There were 16 cases (61.1 per cent) showing moderate to marked improvement.

Laboratory Changes:

The sputum was changed from positive to negative (“converted,” “reverted”) in 11 cases (44 per cent) out of 25. One case had a lobectomy and was treated after the operation but was never positive after the lobectomy. The other 14 cases remained positive, but the quantity of sputum was reduced in practically all.

Resistance of Bacilli:

Of the 14 cases tested for virulence, three did not have sufficient growth for testing; one was resistant to 0.2 mcgms.; four to 1 mcg.; one partially to 5 mcgms.; and five completely resistant to 5 mcg. From experience, it has been observed that partial resistance does not necessarily mean that clinical results may not still be obtained. In the 11 that were tested, however, five (45.5 per cent) were completely resistant and were beyond the point where any more treatment would give material benefit. If we add the one case partially resistant to 5 mcgs. it makes six cases (55.6 per cent) with a resistance that practically prohibits further treatment.

The Blood Cytology:

There was a consistent change in the majority of cases from an inflammatory type of blood cytology towards a normal. There was slight increase of red cells and hemoglobin, a decrease of the white blood count, and a marked lowering of the sedimentation rate.

The Blood Chemistry:

The blood chemistry was noted for the change towards normal of the albumen-globulin ratio. There were 15 of 20 cases (75 per cent) showing
an increased trend towards normal with five cases (25 per cent) a decrease in ratio. The general trend of an increase in albumen and a decrease in globulin in healing is an old and reliable index of improvement.

The blood urea nitrogen in almost all cases showed a rise in the beginning from 15 to 50 per cent, but usually levelled off or decreased after a few months of treatment and nothing of a serious nature developed in any of the cases treated.

Isoniazid with Streptomycin:

Of the 10 cases treated with streptomycin and INAH, the results were more impressive than when isoniazid was used alone. All cases were far advanced and three fourths gms. streptomycin was given intramuscularly twice a week.

The number of cases were too few to do anything more than generalize. Surely there was nothing to be said against the combination as no unusual toxicity was noted and the results were as good or better than those treated in the first series.

There was improvement in all 10 cases with nine gaining more than 10 pounds in weight; one less than 10 pounds while only one lost weight.

The blood cytology changed for the better in almost every case. The red cells and hemoglobin increased, the white cells decreased, and the sedimentation rate decreased. The blood chemistry revealed a favorable change in the protein quotient in all eight cases tested.

FIGURE 7: Same as Figure 3 on March 18, 1953 after seven months treatment with INAH and 11 months of SM and PAS. The annular shadow has disappeared from view but the upper wall may still be outlined.
Five cases were negative on gastric lavage after the treatment, one positive on culture and four positive on smear.

Radiologically, all 10 cases showed improvement; six marked, one moderate, and three slight.

The resistance studies were done on four of the five cases on which positive cultures were obtained. All were sensitive to 10 mcgms. streptomycin. Two were resistant to 1 mcg. INAH and two (50 per cent) to 5 mcgms. of INAH, agreement with the report of Ferebee and Long. There was no striking decrease in the resistance as a result of the presence of streptomycin although the number was too small to be of significance.

Discussion:

A few observations were recorded in this study that are worthy of comment. First, is the generally favorable results in cases treated with INAH and the lack of serious toxic effects. No permanent toxicity was found, but one case had a marked urticaria that disappeared after desensitization. The results were comparable to those treated with streptomycin, but probably were not as good as streptomycin and PAS although in the small series it was difficult to determine. The addition of streptomycin seemed to enhance the results and afford a good combination—as good or better—than streptomycin and PAS.

If the INAH does protect against resistance to streptomycin according to the reports it will be a great advantage as INAH is much easier to administer than PAS. Perhaps it will be better to give all three drugs together.

There is no question but that the death rate has been lowered for tuberculosis by streptomycin, PAS and INAH, but how much, has been a true lowering of death rate or a temporary prolongation of life, is not definite. It is probable that both exist.

A most important report has been given by Klée from the Wuppertal-Elberfeld Municipal Hospital, Germany, to the effect that the death rate of the hospital was around 36 per cent in 1938, in 1940 it rose to 43.3 per cent and to 46.6 per cent in 1941 during the War. In 1946, after the war was over it dropped to 39.2 per cent then plunged to 12.3 per cent by 1949 (streptomycin, PAS and tibione effect). Then it rose to 13.3 per cent in 1949 and plunged again to 0.9 per cent in 1952 after INAH had been introduced. It is difficult to see how a fall from 39.3 to 0.9 per cent in six years can be anything else but a true increase in life saving.

It has been estimated that deaths from clinical tuberculosis have decreased from near 100 per cent 75 years ago to only about 25 per cent today—and it is still decreasing! Perhaps we shall soon see the figures drop to 20, 10 per cent or to a stable figure that can be considered an "irreducible minimum" like those found in many other infectious diseases prevalent in the last century.

We are finally able to confirm what was suspected when INAH was first heralded in such glowing terms, viz: that the first flush of success was probably deceiving. It is now certain that the drug alone soon "burns out"
its usefulness. It must be used to the greatest advantage before resistance develops by saving it till the most opportune time, or by combining it with other agents to effect a mutual reduction in resistance. Undoubtedly there will be further improvements made. It is clear that the drug should not be given without careful supervision. Otherwise the "ammunition" will be wasted before the "enemy" is subdued. In fact the "ammunition" will be worse than wasted, because the premature and uncontrolled use of the drug only allows the "enemy" to develop a complete resistance after which the drug becomes useless.

These facts are presented to warn those who would go their own way in treatment and take the drug simply because it is easily self administered. It is even more important that physicians should learn how to get the maximum results with the drug. "Home Treatment" for a patient who is found to have active tuberculosis is, therefore, not at all wise unless every control measure is used that is employed in the hospital. Since few patients can be treated as in a hospital the admonition is not to take home treatment at all during the early phases of active disease!

There comes a time, however, when the patient will capitalize on the saving brought about by good management. After the acute disease has been suppressed, all symptoms have gone, the weight has increased, the x-ray film shadows are gone or disappearing and the patient is "negative" for virulent tubercle bacilli, the patient may be released weeks and even months before he otherwise would have been and treated at home by competent physicians. The time is here when the follow-up of such patients must be done in competent out-patient clinics or by the Health Department.

Still more saving of time is being made by a skillful application of surgery. When the drugs have cleared up most of the disease and cavities or masses still remain, surgery is a saving grace that has no equal in eradicating the unhealed residues just as the older surgeons would curette a carbuncle. Recovery from the surgery requires about a third the time that is required to heal the disease without it, besides surgery is more final in effecting a cure of the process.

A word of warning should also be issued to those who administer Recalcitrant Patient Laws. Before any commitment order is issued it should be made certain that the patient has bacilli in sputum that will kill guinea pigs. The new drugs are producing many bacilli that can be demonstrated on smear but they are not virulent or will otherwise not cause infection in animals, in spite of the fact that the x-ray film may show infiltrates. If it can't be proved that the secretions coming from the patient will cause infection, it seems clear that no patient can be forcibly confined irrespective of the x-ray film shadows or even the staining reactions. A test on this type of case might well cause the law to become invalid.

SUMMARY

1) An attempt has been made to place isoniazid in its proper therapeutic position and to present the theories of its action.

2) This objective has been aided by a study of the effect of INAH in the
treatment of 26 patients with pulmonary tuberculosis, as well as the treatment of 10 tuberculous patients with combined INAH and streptomycin.

3) The indications for treatment may be briefly stated as proper in all cases having acute, infiltrative components in the process. The more acute the lesions, the better the results, with a decreasing effectiveness as fibrosis exists or develops.

4) In cases still having bacilli present in the sputum isoniazid alone in 8 to 12 weeks time causes a crippling resistance to develop in the bacilli in over half the cases but with streptomycin added the resistance is reduced to less than 20 per cent.

5) According to the best information, isoniazid causes a reduction in resistance of bacilli to streptomycin, but there is still twice the resistance that develops when PAS is used.

6) The effect of INAH may be divided into two components, viz: the effect on the bacillus and the effect on the patient. The effect on the bacillus is only superficially understood at present, except that they soon cease to multiply and tend to gradually disappear from the lesions. The action is not bacteriocidal but probably the metabolism of the bacillus is suspended. Eleven of 25 cases of the first series (44 per cent) were changed from positive to negative. After two months, resistance (to five mcgms. of INAH per ml.) appears in over 50 per cent of the cultures.

7) The properly selected patient reacts rather promptly in what may prove to be a combination of non-specific stimulation and the result of the removal of toxicity of the infection. As a result, the patient promptly feels better, at times almost exhilarated. The temperature and pulse begin to approach, the normal, the appetite improves, with a resulting gain in weight, and the x-ray and laboratory findings generally show a corresponding favorable change. Many times the patient feels better and desires to take exercise more than the anatomical changes of the disease warrants.

8) In the 26 cases treated with isoniazid there was a general and unmistakable improvement in all but one. In 12 there was marked improvement, in nine moderate improvement, and in four slight improvement. There was no noticeable sex and race differences.

9) The weight changes paralleled the clinical findings. There were 12 patients who gained over 20 pounds; five gained between 10 and 20 pounds and eight gained between one and 10 pounds.

10) Radiological change lagged slightly behind clinical changes. There were 11 that showed marked improvement; five moderate improvement; and five slight improvement. Two showed no change and three showed slight progression of the lesions. Moderate to marked improvement was observed in 16 cases (61.6 per cent).

11) The addition of streptomycin to the INAH treatment in 10 cases had no outstanding changes over those found for INAH. Nine (90 per cent) gained more than 10 pounds in weight and all improved as shown by clinical, x-ray film, and laboratory findings. These changes were generally similar, but more marked, than those listed for INAH alone.

12) Of four cases (40 per cent) of the combined therapy on which bacilli
could be tested all were sensitive to 10 mcgms. streptomycin, two were resistant to 1 mcgm. INAH and two (50 per cent) to 5 mcgms. The number was too small to be significant. Other studies reveal a resistance of less than 20 per cent.

13) In spite of rather dramatic effects of isoniazid treatment, patients should be hospitalized and treated by a full drug regimen during the acute stages of the disease, but many weeks and months may be saved toward the end of treatment when the patient may be treated at home under proper supervision.

14) Patients having residual infiltrates and heavy walled cavities may also have many months cut off of hospital stage by removal of the disease process by surgical excision or collapse along with, or after drug and antibiotic therapy.

RESUMEN

1) Se intenta colocar la isoniacida en su posición adecuada en la terapéutica y presentar las teorías sobre su acción.

2) Este objetivo, ha sido accesible gracias al estudio de 26 enfermos con INAH, así como el estudio de 10 enfermos tuberculosos con INAH combinada con estreptomicina.

3) Las indicaciones para el tratamiento, pueden ser brevemente consideradas como adecuadas en todos los casos con lesiones agudas e infiltrativas. Mientras más agudas son las lesiones, mejores son los resultados, decreciendo su efectividad a medida que se presenta o se desarrolla la fibrosis.

4) En los casos en que hay bacilos en los esputos, la isoniacida sola, causa una aparición de resistencia de las 8 a 12 semanas en la mitad de los casos, pero si se agrega la estreptomicina la resistencia se reduce a menos del 20 por ciento.

5) La isoniacida permite el desarrollo de la resistencia a la estreptomicina en casi la mitad de los casos en comparación con el PAS. Esta combinación por tanto, es la mejor referida hasta ahora.

6) El efecto de la INAH, puede dividirse en dos componentes: El efecto sobre el bacilo y el efecto sobre el enfermo. El efecto sobre el bacilo es sólo superficialmente comprendido hasta hoy; sólo se sabe que el bacilo cesa de multiplicarse y tiende a desaparecer gradualmente de las lesiones. La acción no es bactericida, sino probablemente se afecta el metabolismo del bacilo, suspendiéndolo. Once de 25 casos en la primera serie (44 por ciento) cambiaron de positivos a negativos. Después de dos meses, la resistencia (a 4 microgramos de INAH por ml.) aparece en el 50 por ciento de los cultivos.

7) El enfermo escogido adecuadamente reacciona pronto de manera que puede considerarse demostrativa de que existe una combinación de estimulo no específico y el resultado de la supresión de la infección. Como resultado el enfermo se siente pronto bien, a veces eufórico. La temperatura y el pulso, empiezan a aproximarse a lo normal, el apetito mejora con resultante aumento de peso y a los rayos X y al laboratorio los hallazgos
muestran un cambio favorable correlativo. Muchas veces el enfermo se siente mejor y desea hacer ejercicio más de lo que los cambios anatómicos permitirían.

8) Sólo en uno de los 26 casos, dejó de presentarse una mejoria general inconfundible. En 12, hubo marcada mejoria, en nueve moderada y en 4 ligera mejoria. No hubo diferencias apreciables en las diferentes razas y sexos.

9) Los cambios en el peso, son paralelos a los cambios clínicos. Hubo 12 enfermos que aumentaron más de 20 libras; 5 aumentaron entre 10 y 20 libras, y ocho sólo entre una y diez.

10) El cambio radiológico fue ligeramente más lento que el clínico. Hubo 11 que mostraron mejoria marcada, cinco con moderada y cinco con ligera mejoria. Dos no mostraron cambio y tres tuvieron ligero empeoramiento. En 16 casos (61 por ciento) se observó de moderada a marcada mejoria.

11) El agregar estreptomicina a la INAH en 10 casos, no produjo notables cambios sobre los encontrados con solo la INAH. Nueve (90 por ciento) subieron más de 10 libras de peso y todos mejoraron según los hallazgos clínicos, radiológicos y de laboratorio. Estos cambios, fueron similares, pero más marcados que los señalados para la INAH sola.

12) De cuatro casos (40 por ciento) entre los de tratamiento combinado, en los que el bacilo pudo ser estudiado, todos eran sensibles para 10 microgrs. de estreptomicina, dos eran resistentes a un microgr. de INAH y dos (50 por ciento) a cinco microgrs. El número fué muy pequeño para tener significación. Otros estudios revelan resistencias de menos de 20 por ciento.

13) A pesar del efecto dramático del tratamiento con la isoniazida, los enfermos deben ser hospitalizados y tratados con un régimen completo de drogas durante las etapas agudas de la enfermedad, pero muchas semanas y meses pueden ahorrase para llevar al enfermo al fin, cuando el mismo, pueda tratarse en su domicilio bajo adecuada vigilancia.

14) Los enfermos que tienen infiltrados residuales y cavidades con paredes gruesas, pueden también ahorrarse muchos meses de estancia en el hospital para hacerse resección o colapso quirúrgico tratándose al mismo tiempo o después, con los antibióticos y estas drogas.

RESUMÉ

1) Les auteurs font un effort pour mettre l'isoniazide à sa place exacte dans la thérapeutique et pour étudier le mécanisme de son action.

2) Cet objectif a été favorisé par une étude sur l'effet de l'isoniazide dans le traitement de 26 malades, atteints de tuberculose pulmonaire, ainsi que par le traitement de dix tuberculeux où furent associée l'isoniazide et la streptomycine.

3) Les indications du traitement peuvent être rapidement établies comme convenant à tous les cas alégu, avec processus infiltratif. Plus les lésions sont algues, plus les résultats sont bons, avec une diminution des lésions des qu'il existe une tuberculose fibreuse on dès qu'elle se développe.

4) Dans les cas qui ont encore des bacilles dans leur expectoration, l'isoniazide administré isolément détermine en huit à douze semaines une
résistance au développement des bacilles dans plus de la moitié des cas, mais lorsque la streptomycine est associée, cette résistance se réduit à moins de 20% des cas.

5) L'isoniazide associée à la streptomycine détermine environ deux fois moins de résistance que le P.A.S. La combinaison streptomycine-isoniazide est ainsi la meilleure connue jusqu'à présent.

6) L'effet de l'isoniazide doit se diviser en deux parties: l'effet sur le bacille, l'effet sur le malade. L'action sur les bacilles est connue jusqu'à présent seulement d'une façon superficielle. On sait simplement que très vite, ils cessent de se multiplier, et qu'ils tendent à disparaître progressivement des lésions. L'action n'est pas bactéricide, mais vraisemblablement, il y a un trouble profond du métabolisme du bacille. Onze des vingt-cinq cas de la première série, soit 44%, vinrent l'expectoration se transformer de positive en negative. Aprés deux mois, la résistance (jusqu'à 5 gammas d'isoniazide par cc.) apparut dans plus de 50% des cultures.

7) Les malades bien choisis eurent des réactions assez rapides qui semblent indiquer qu'il y à combinaison d'une stimulation non spécifique et de la disparition de la toxicité de l'infection. Le malade très rapidement se sent mieux, parfois même tout à fait euphorique, la température et le pouls commencent à tendre à la normale, l'appétit s'améliore avec une augmentation de poids, et les constatations radiologiques et biologiques en général montrent parallèlement des modifications favorables. Souvent le malade se sent mieux, et désire reprendre une activité plus importante que ne le permettent les modifications anatomiques des lésions.

8) Dans 26 cas qui ont été traités avec l'isoniazide, il y à d'une façon générale amélioration incontestable dans tous les cas sauf un. Dans douze cas, il y eut une amélioration nette, dans neuf cas modérée, et dans quatre cas légère. Il n'y eut aucune différence notable selon le sexe ou la race.

9) Le poids se modifa parallèlement aux constations cliniques. Douze malades augmentèrent de plus de 20 livres, cinq augmentèrent de 10 à 20 livres, et huit entre une et dix livres.

10) Les modifications radiologiques se montrent assez inférieures aux modifications cliniques. Onze malades eurent une amélioration nette, cinq une amélioration modérée, et cinq autres une amélioration légère. Chez deux malades, il n'y eut aucune modification, et trois autres montrent une légère aggravation des lésions. Chez 16 malades (61%) on nota une amélioration oscillant de l'amélioration modérée à l'amélioration très nette.

11) L'association de streptomycine chez dix malades ne donna pas une modification considérable des constatations faites avec l'isoniazide isolé. Neuf d'entre eux (90%) augmentèrent de plus de 10 livres, et tous s'améliorèrent cliniquement, radiologiquement, et biologiquement. Cette évolution généralement fut similaire et non supérieure à celle qui fut obtenue par l'isoniazide isolément.

12) Parmi ces cas où la thérapeutique associée fut instituée, quatre (40%) pour lesquels fut mesurée la résistance des bacilles, tous se montrèrent sensibles à 10 gammas de streptomycine, deux furent résistants à un gamma d'isoniazide et deux (50%) à cinq gammas d'isoniazide. Le nombre
est trop petit pour avoir une valeur quelconque. D'autres études montrent une résistance de moins de 20%.

13) Malgré l'effet relativement sensationnel du traitement par l'isoniazide, les malades devraient être hospitalisés et traités par le régime complet pendant la phase aigue de la maladie mais le malade peut ensuite être traité pendant de nombreuses semaines et de nombreux mois vers la fin de ce traitement, à domicile à condition d'être bien contrôlé.

14) Les malades ayant des infiltrats résiduels et des cavités à parois épaisses, peuvent également avoir leur temps d'hospitalisation considérablement réduit en supprimant la lésion par exérèse chirurgicale, par collapsus, avec l'aide de la chimiothérapie et du traitement antibiotique.

REFERENCES
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10 Steenken and Wollinsky: "Report of Twelfth Conference on the Chemotherapy of Tuberculosis—and Certain Others, of the Veterans Administration, Army and Navy, at Atlanta, Georgia, February 9-12, 1953.