ANTITHYROID SUBSTANCES IN THE TREATMENT OF LEPROSY

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This is a preliminary report of experience with antithyroid medicaments in the treatment of leprosy over a period of nearly eight years. In this paper are described in some detail four representative cases treated with Tapazole (methimazole, Lilly) as the principal therapeutic agent.

ORIGINAL OBSERVATION

In October 1952, I examined for the first time a patient affected simultaneously with thyrotoxicosis and leprosy. The lesions were of the indeterminate type. A sister had leprosy which I had treated in past years.

The patient's lesions were erythematous, hypopigmented patches on the back and the upper and lower extremities, and were bacteriologically positive for acid-fast organisms. These lesions had appeared two months previously, and at first were localized on the legs. In addition, she presented a notable degree of exophthalmos, tachycardia of 130 beats per minute, excessive sweating, tremor especially of the upper extremities, anxiety, and fear out of proportion to the appearance of the skin lesions. According to her history, she had taken Lugol's solution, prescribed for the thyrotoxicosis, for 10 days when the first skin lesions were noted. They increased in number, and because of her sister's experience she came for examination.

Her endocrine condition, however, most urgently required therapy and, after endocrinologic consultation, I decided to use propylthiouracil. The drug was started in relatively small doses to test the patient's tolerance. Needless to say, the patient took no more Lugol's solution. Although she was asked to return in one month, she did not return until after two months as her endocrinologist had taken the initiative to continue the treatment in proper dosage. Upon examination at this time it was apparent that her granular "storm" had subsided significantly, and also that her leprosy manifestations had improved. She was advised to continue treatment exclusively with propylthiouracil. Motivated entirely by curiosity, I refrained from using any known antileprosy medication.

Six months later, her thyrotoxicosis showed further clinical improvement, and the spots characteristic of indeterminate leprosy then appeared residual—greatly reduced in size, pigmented, and bacteriologically negative.

Because of this observation of clinical and bacteriologic improvement in a case of leprosy, and considering the well-known deleterious effect of iodide on leprous manifestations ([5]), and the possibly significant fact that antithyroid drugs decrease protein-bound iodide in the blood ([4]), I was led to test further the effects of antithyroid preparations in the treatment of other cases of leprosy in which there were no thyroid complications.

Between 1953 and 1958, I treated a total of 69 cases of leprosy with relatively low dosages of antithyroid drugs, including propylthiouracil and Tapazole, administering them as adjuvants to the sulfones. The dosage of the antithyroid drug employed was slowly increased as its continued use gave sufficient confidence to permit manipulation of the

dosage. Forty-two of these cases showed satisfactory control of the disease. In May 1958, this series of cases was reported at the Primer Congreso Nacional de Leprología, in Cartagena, Colombia.

The initial use of the antithyroid drug only as adjuvant to the sulfones was then changed to its use as the basic treatment for leprosy. By May 1960, the antithyroid drugs had been used in a total of 236 cases. This experience had provided information on the most effective dosage schedules, and had demonstrated from the clinical point of view the superiority of Tapazole among the various antithyroid agents employed. This drug has been said to be about ten times as potent as propylthiouracil in antithyroid activity ([1, 2, 6, 7]). During the last two years, I have continued to treat most new leprosy cases with this medicament alone.

CASE REPORTS

Case 1. M.F., a 38-year-old male with leonine infiltrations of the forehead, cheeks, chin, and sides of the nose, was first seen on March 23, 1959. Both ears were totally infiltrated with confluent lepromas (Fig. 1). Leprosy lesions covered the chest, the hypochondrium, the epigastric area, the periumbilical region, and all of the arms except the anterior aspects. In the lumbar region there were individual tubercles in great quantity. On both gluteal regions there were scars, with some places surrounded by atrophic skin and other places infiltrated with confluent lepromas. On the fronts of both thighs there were a few reactional erythematous nodules. On the back of the lower third of both legs was a severe desquamative process with alopecia, anhidrosis, and atrophy. The patient suffered from frequent nose-bleed, the septum of the nose being ulcerated. The results of bacteriologic examinations for acid-fast organisms were strongly positive (4+).

Treatment consisted of 30 mgm. (6 tablets, 5 mgm. each) of Tapazole daily, divided into 3 equal doses administered after breakfast, after lunch, and at bedtime. Complete diet included a quart of milk daily.

Thirty-five days later, April 28, 1959, the infiltration of the forehead, cheeks, chin, nose, and ears had virtually disappeared (Fig. 2). There remained only sparse, smooth lepromas covered with hyperpigmented and atrophic skin. The lepromatous infiltrations that had been on the chest, hypochondrium, and epigastric area also had disappeared, leaving hyperpigmented spots corresponding to the sites of the most pronounced infiltrations. The same degree of improvement was seen in all other areas. The nosebleeds had ceased, and the septum was in the process of cicatrization. Only the ears were bacteriologically positive (2+), whereas tests were negative from the back where there had been lepromas in the previous month.

On January 18, 1960, when the patient came for a periodical examination, it was found that the dosage of Tapazole had been reduced to 15 mgm. daily since June 15, 1959 and had been stopped two months previously, when a nurse at the hospital gave him diaminodiphenyl sulfone (DDS), one tablet a day. There were no changes in appearance of the previous lesions or microscopic findings since the last visit, but the patient complained that he did not feel well. Treatment with 15 mgm. of Tapazole daily was resumed for 30 days, after which the patient discontinued the medication. At the end of a week without any treatment, fever appeared and lasted for about three weeks. When I next examined the patient, on April 11, 1960, he had no fever but had lost weight. There were no new lepromas or reactional lesions, but in several places there were signs of regression of erythema nodosum. A lesion of the ear was bacteriologically positive (1+), the bacilli granular, without globi. Tapazole was prescribed, 40 mgm. a day.

When last examined on April 26, 1960, the patient had regained 1.5 kgm. in weight and felt well. The white blood cell count was normal. There were no reactional lesions or lepromas on any part of the body. Only areas of intense localized hyperpigmentation

were observed at the sites of former lepromas. Less intense, diffuse pigmentation was observed at some other sites of previous infiltrations. Bacilli were very scarce and granular. At present, the patient is continuing treatment with 30 mgm. of Tapazole daily.

CASE 2. C.L., female, reported onset of the disease in December 1955, with fever and erythematous macules on the back and legs. This episode was repeated on several occasions. She was treated with different types of antibiotics by general practitioners. Laboratory studies were negative except for leukocytosis and slight anemia.

Eleven months later she became pregnant and, for the first time, lesions of erythema nodosum type appeared on the upper extremities. She had neuritis in the left foot. Potassium iodide was prescribed by a herb doctor and the clinical condition worsened. Treatment was discontinued.

A year later, in October 1957, febrile reactions appeared, and erythematous macules on the face, chest, back, and upper and lower extremities. An obstructive rhinitis commenced. A biopsy specimen was taken from the internal aspect of the lower third of the left thigh. Histologic examination revealed lepromatous infiltrations. Treatment with DDS, ½ tablet two times a day, was given. Fifteen days afterwards, dosage was increased to 200 mgm. a day for a fortnight, following which lepra reaction occurred which lasted for a month and a half.

I examined the patient on March 1, 1959. There were diffuse erythematous macules and infiltrations of the cheeks with impetigo (Fig. 3). Varying degrees of anesthesia or dysesthesia were observed in the hands, thighs, and legs. Erythematous macules were found on the left arm, the legs, and the gluteal regions. On the arms, there could also be seen subcutaneous nodular lesions which were hard, well-defined, and relatively isolated. The laboratory confirmed the presence of bacilli, and a diagnosis of lepromatous leprosy was made. Treatment was initiated with propylthiouracil, 3 tablets of 50 mgm. each a day for 25 days. The patient showed improvement of her lesions, but due to allergic rash and fever the medication was discontinued.

On May 10, 1959, treatment with 5 mgm. of Tapazole daily was started, the dose increased after a few days to 10 mgm. daily. Complete diet included a large amount of milk. By June 17, 1959, her condition was very satisfactory. The edema and subcutaneous nodules were disappearing, and the violaceous appearance of the extremities was clearing up. The impetigo of the cheeks was gone. By August 13, 1959, all of the symptoms originally seen had disappeared. Fig. 4 presents her appearance on January 15, 1960. The laboratory findings were negative for bacilli. On April 21, 1960, no changes were found. The patient had continued the Tapazole treatment.

CASE 3. P.L.E., a 30-year-old male with lepromatous leprosy of almost three years' duration. He had previously been treated with Diamidin, Nidrazid, and vitamin E. When I first examined him on September 1, 1959, he had fever (104°F), infiltrations of the face and ears, and erythematous edematous patches on the upper and lower extremities, chest, abdomen, back, and gluteal regions (Fig. 5). The lepromatous areas were in general of small or medium size, irregular in outline, well delimited, and elevated above the healthy surrounding surface. The lesions were warm to touch and hard. Bacteriologic smears were strongly positive for bacilli. It was a case of acute lepromatosis.

In accordance with our experience we gave prednisone (Meticorten) along with the antithyroid drug for one week. The patient was started on 40 mgm. of Tapazole daily in 4 divided doses (2 tablets each). During the second week the dose of Tapazole was maintained and that of Meticorten progressively diminished. Fifteen days after treatment was started, the lepromatous process was effectively arrested. The microscopic findings had diminished abruptly in the two weeks time. Fig. 6 represents his appearance on December 1, 1959.

From September 16 until October 27, 1959, the patient took 5 tablets of Tapazole daily. He was examined for the third time on the latter date, and the dose of Tapazole was diminished to 3 tablets daily. That was continued until March 21, 1960, when the patient commenced a febrile reaction with an eruption of several erythematous macules. The leukocyte count was normal and laboratory examination for bacilli negative. Tapazole was increased to 5 tablets daily, which was maintained. Diet included one quart of milk daily. Microscopic examinations continued to be negative, and there were no signs of active leprosy.

CASE 4. Z.J.L., was a 27-year-old laborer, single, who had shown symptoms of the disease since the age of 19 but had never had a lepra reaction. Recently he had become worse, and on October 6, 1958, he presented himself with marked lepromatous infiltrations of the lower half of the forehead, both cheeks, chin, nose, and ears, in which moreover there were numerous confluent lepromas (Fig. 7). There was obstructive rhinitis. Scars of lepromas were noted on the upper extremities, small individual lepromas on the lower extremities, and undefined erythematous purple pigmented macules on the gluteal region. The back and the rest of the body were normal. He had paresthesias of the feet, and anesthesia of the middle third of the legs and the anterior parts of both feet. There was alopecia at the extremities of the eyebrows.

The patient was treated with 5 tablets Tapazole until March 30, 1959; the diet included a quart of milk daily. By January 26, 1959, the patient had experienced a remarkable transformation (Fig. 8). He did not have fever, and the bacterial index had decreased abruptly.

By March 30, 1959, the patient had taken 700 tablets of Tapazole, and the drug was well tolerated. From that date to April 3, 1960 he took 500 more tablets. The present maintenance dosage is one 5 mgm. tablet daily. He shows no signs of hypothyroidism, nor mental alterations. Bacteriologic smears are negative.

DISCUSSION

The distribution of leprosy and endemic goiter in the various countries of the world is, in general, in opposition. In regions severely affected by leprosy there is a low incidence of endemic goiter, and vice versa. This thesis should be considered from a general point of view, even though in Central Africa there is a high incidence of both diseases, because one notices that in that region the percentages of the benign tuberculoid form are very high, sometimes as high as 90 per cent. In zones of high incidence of leprosy such as India, China, and the East Indies, the large intake of iodine-containing algae in the food is to be noted, and in other areas of increased incidence of leprosy there is a high consumption of fish with high iodine content. In the regions of the world with low incidence of leprosy there is often consumption, equally notable, of antithyroid vegetables such as turnip or rutabaga among others, containing 1-5-vinyl, 2-thiooxazolidone ([3]).

In the biochemical picture of leprosy we find a series of truly remarkable analogies with the biochemical picture of thyrotoxicosis:

DESCRIPTION OF PICTURES

FIG. 1. Case 1, lepromatous leprosy in a 38-year-old male, before Tapazole treatment.

FIG. 2. Case 1, showing virtual disappearance of the lesions of face and ears after 35 days of treatment.

FIG. 3. Case 2, a female patient with lepromatous leprosy of 3 years duration, before treatment. Treatment was begun with propylthiouracil for 25 days, and then because of reaction was changed to Tapazole in low dosage.

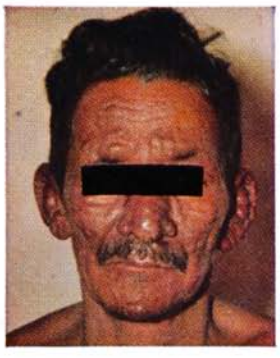
FIG. 4. Case 2, showing marked improvement 8 months after Tapazole treatment was begun.

FIG. 5. Case 3, a 30-year-old male with leprosy of nearly 3 years duration, in a state of acute lepromatosis, before treatment (prednisone alone for a week, then beginning of Tapazole).

FIG. 6. Case 3, appearance after 3 months of treatment.

FIG. 7. Case 4, a 27-year-old male with lepromatous leprosy, the disease of some 8 years duration, before treatment.

FIG. 8. Case 4, transformation after less than 4 months treatment with Tapazole.



← Figure 1. *Infiltrations of forehead, cheeks, chin, and nose and confluent lepromas in both ears.*

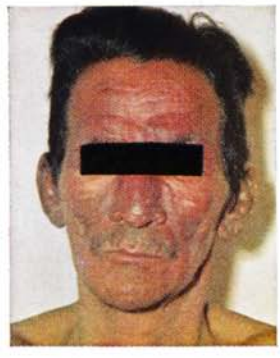
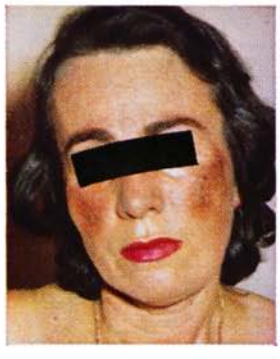


Figure 2. *Thirty-five days after treatment.* →



← Figure 3. *Diffuse erythematous macules and infiltrations of cheeks with impetigo.*

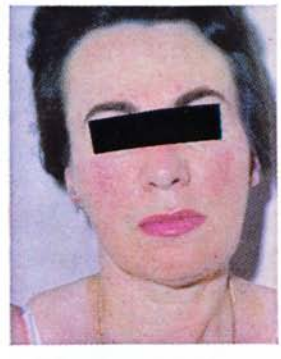
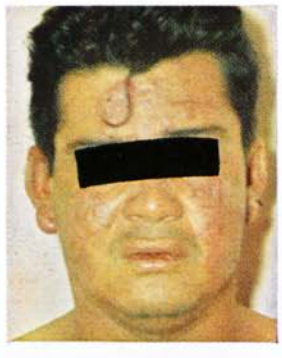


Figure 4. *Skin lesions have disappeared.* →



← Figure 5. *Infiltrations of the face and ears.*

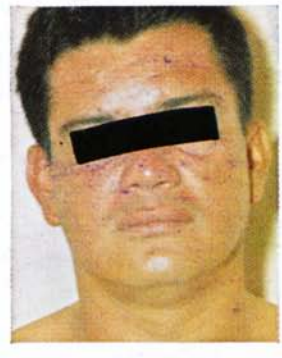
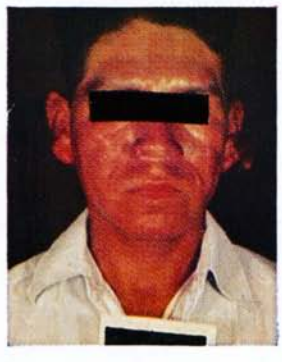


Figure 6. *After three months of therapy with Tapazole.* →



← Figure 7. *Lepromatous infiltrations of the lower half of the forehead.*

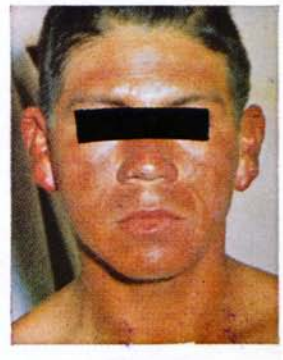


Figure 8. *Remarkable transformation after fifteen weeks on Tapazole.* →

(1) figures for the serum cholesterol equally low; (2) analogous diminution of the diffusible calcium; (3) elevated glycemia; (4) diminished alkaline reserve; (5) increased globulin; (6) urea generally reduced; (7) sedimentation rate increased; (8) low glutathione; and (9) diminished ascorbic acid.

I believe that leprosy as well as hyperthyroidism is a constitutional disorder and following the words of Bernard Ficarra we can conclude that the clinical signs of this disease "are merely an outward sign of a hidden underlying constitutional disturbance with many ramifications."

CONCLUSIONS

Extensive use of various antithyroid preparations during nearly eight years, and in a total of 236 leprosy cases, may open a new road for the treatment of that disease. Four representative cases, treated with different dosages of Tapazole, which have improved remarkably in short periods of time have been presented. With these four clinical cases we have tried to demonstrate the various experiences which we have had in the treatment of leprosy with Tapazole as an example of the antithyroid drugs. A careful study of these treatments will reveal the effects obtained and the errors made, which would be helpful in their future application.

CONCLUSIONES

El uso extenso que se ha hecho en Cali, Colombia, de varios antitiroideos durante ocho años y en un total, hasta le fecha, de 236 leprosos, abre un camino nuevo en el tratamiento de la enfermedad de Hansen. Se presentan cuatro casos representativos tratados con diferentes dosificaciones de Tapazol que obtuvieron una notable mejoría en un corto período de tiempo. Con estos cuatro casos clínicos hemos tratado de demostrar las diversas experiencias que hemos tenido en el tratamiento de la lepra por medio del Tapazol, como ejemplo de las drogas antitiroideas. De un estudio cuidadoso de los tratamientos expuestos podrán deducirse los efectos obtenidos y los errores que hemos cometido, lo cual será de provecho para su aplicación futura.

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