

THE TREATMENT OF LEPRA REACTION WITH AN AZULENE DERIVATIVE, "AZ-8"

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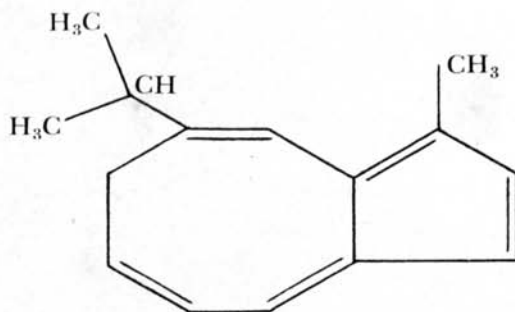
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The multiplicity of drugs of diverse chemical composition prescribed with the object of suppressing or mitigating reactions in lepromatous patients under treatment is in itself evidence that the panacea has not yet been found (⁶).

A trial was therefore undertaken with a drug which has received favorable notice, in over a hundred publications, in respect of its anti-inflammatory and anti-allergic properties, a drug which has been used with some success in tuberculosis and in various acute and chronic dermatoses. This compound is an azulene derivative known as "AZ-8" (Beris Laboratories, Zurich).

The only paper concerning the use of this drug in lepra reaction is by de Oliveira Lima (⁷), who reported that 29 out of 40 lepromatous patients suffering from long-standing lepra reaction improved after treatment with it.

Chemically, AZ-8 is 1,4, dimethyl-7-isopropyl azulene, and has the following structural formula:



The azulenes are characterized by possessing two condensed rings, of five and seven carbon atoms. An azulene occurring naturally in vegetable oil figures is a popular cure in some countries. We refer to the common or Roman camomile oil (*Oleum anthemidis*, B.P.C.), obtained from the dried flowerheads of *Anthemis nobilis* L. by distillation. There is also the German or wild camomile oil, which is made from *Matricaria chamomilla*. Essence of manzanilla, which also contains an azulene, is used popularly in Spain for its tonic and febrifuge properties.

Adequate toxicologic and pharmacologic investigations have been carried out concerning the azulenes in general and AZ-8 in particular.

The absence of toxic effects in the experimental animal and in patients suffering from tuberculosis or other diseases suggested that the drug would probably be without aggravating effect on leprosy reaction.

AZ-8 is said, by Barton and Wendler (²) and by Gözsy and Kató (^{4, 5}), to stimulate the leucocytes and the phagocytic activity of the monocytes. Its action extends to the entire reticuloendothelial system, including the endothelial cells of the cutaneous blood vessels (⁵). It combines readily with oxygen (¹).

THE TRIAL AT UZUAKOLI

All lepromatous patients in the Settlement actually suffering from persistent leprosy reaction, and all those who developed reactions after the trial had begun, were given treatment with AZ-8. Antireaction measures already in use were discontinued, and no other measures were instituted concurrently. The majority of the patients were ambulant, but those whose general condition required it were admitted to the hospital.

Patients.—In all, 23 patients, 20 of them males, were treated with AZ-8. Their ages ranged from 9 to 55, with an average of 23 years. All were suffering from lepromatous leprosy, except one patient who had reactional borderline leprosy, bacteriologically positive. The gravity of the disease is indicated by the presence of multiple lepromata in 15 patients, and of diffuse infiltration in 16.

The patients had been treated with a variety of antileprosy drugs, alone and in combination (dapsons, Thiambutosine, Ditophal), for the following periods before the onset of the reactional state:

Under 3 months:	3 patients
3- 6 months:	3 patients
7-12 months:	8 patients
13-17 months:	2 patients
18-24 months:	5 patients
Over 24 months:	2 patients

The reactional state was assessed as slight in 3, moderate in 13, and severe in 7, and had persisted for the following periods:

Under 3 months:	6 patients
3- 6 months:	4 patients
7-12 months:	4 patients
13-17 months:	2 patients
18-24 months:	1 patient
Over 24 months:	3 patients

The reactional state of 17 of these patients had been more or less controlled by a succession or a combination of drugs generally used for the condition. By this means it was generally possible to continue antileprosy treatment in standard or suboptimal dosage. Temporary suppression of antireaction treatment in these patients had been followed by successive crops of erythema nodosum leprosum in the commonly-observed situations; the control was thus temporary and precarious.

The remaining 6 were Settlement patients who experienced their first lepra reactions while the other 17 patients were already undergoing treatment with AZ-8. They were included in the trial as acute reaction cases that had received no specific treatment for the condition, and whose clinical state approximated—especially as regards severity and probable development—that of patients already included on the trial.

Clinical signs of reaction.—The lesions were of three main types: (1) Superficial and raised—often acuminate—pink spots seen typically on the face, the ears, the arms and forearms, and the thighs. (2) Deeper and more diffuse areas of subcutaneous panniculitis appearing on the anterior aspect of the thighs, the anteroexternal aspect of arms and forearms, and the pretibial region. (3) More extensive diffuse and tender swellings of the subcutaneous tissues, often bilaterally symmetrical, and occurring typically on the lower forearms and over the anterior tibial compartment. Elevated temperatures were common; the degree of elevation was in the main proportional to the severity of the reaction.

General signs noted were: adenitis (inguinal, crural, posterior cervical, submental) (9 patients); acute infiltration of helices of ears (11 patients); neuritis of the main peripheral nerve trunks, especially the ulnars in their subcutaneous course; generalized infiltration of the skin; localized infiltrations on the face, trunk, and limbs; subcutaneous fibrosis at sites of election, particularly over the hamstring tendons and the posterior aspect of the lower third of the arm; multiple ulcerations of the indurated, infiltrated, and hyperpigmented integument in these situations; ulceration of nodular lepromata; and acute swelling of testes and of nipples and areolae.

The patients were thus a typical cross-section of the serious types of reaction, which may necessitate more or less prolonged interruption or modification of antileprosy therapy. They constituted a severe test of the drug. If they were benefited, in a demonstrable and convincing fashion unlikely to be spontaneous in such a variable and unpredictable condition, and if antileprosy treatment could be resumed or suboptimal doses increased to standard levels, then a more extensive trial would be justified.

Dosage.—AZ-8 is supplied in ampules of 1 cc. intended for intramuscular injection, each ampule containing 50 mgm. of active substance dissolved in sunflower-seed oil; and in capsules for oral administration containing 20 mgm. Therapeutically, either route may be employed alternatively or concurrently, 8 capsules (160 mgm.) by the mouth being the equivalent of 1 ampule (50 mgm.) by injection.

For the first 10 days the dosage recommended is 2 ampules, or 1 ampule and 8 capsules, or 16 capsules; for the next 30 days, 1 ampule or 8 capsules; thereafter a maintenance dose of 6 capsules daily. The

total daily dosage is given in divided doses, taken after meals.

Side effects.—Apart from slight pain at the site of the initial injections reported by 5 patients out of 22 who received the drug in the deep gluteal region, the injections were well tolerated. There were no infections and no abscess formation.

Signs of toxicity were few and unremarkable. One patient complained of loss of appetite, which returned when treatment with AZ-8 was stopped. Two had slight and transient giddiness. A papular irritating dermatitis developed in 1 patient. One had moderately severe headache after each injection. No instance of nausea, vomiting or intestinal disturbance was reported.

Laboratory findings.—The blood pictures showed no abnormality. Except in 1 patient who had febrile albuminuria accompanied by exacerbation of the reactional condition, the urine was normal chemically and microscopically, assuming the deep blue color of azulene. Complementary laboratory investigations, certain of which are stressed in the literature as affording evidence of the therapeutic efficacy of AZ-8, were carried out without any significant findings coming to light.

In particular, the erythrocyte sedimentation rate remained constantly high (in 9 patients: 40-60), or constantly of medium range (in 2 patients), or constantly low (in 1 patient), and variable in the remaining 11 patients with no definite pattern predominating.

The eosinophil count was generally raised, as is usual in an African population harboring parasites in the blood, lymph and intestines, and subject to various cutaneous irritations. No pattern of increase or decrease in the absolute numbers or the relative proportion of the eosinophils emerged during the period of therapy.

The Velez index, which is an expression of the relative proportions of two-lobed and three-lobed polymorphonuclear leucocytes in the peripheral blood, was determined at regular intervals. A preponderance of two-lobed forms—a "positive Velez index"—is said to be present in active tuberculosis (³). Positive values were found in 34 per cent of the examinations, and negative values in 61 per cent. There was no discernible consistent change from positive to negative or vice versa.

CLINICAL RESULTS

During the course of treatment with AZ-8, the most noticeable feature was the abrupt nature of the changes in the reactional condition of many of the patients. It is well recognized that alternating improvement and deterioration, more or less abrupt and of varying degree, may occur spontaneously in such a group of patients, but the reaction in 17 of them had been observed previously to be severe and reasonably constant. Treatment with AZ-8 seemed to intensify and accelerate any changes that occurred, and perhaps even induced them. The reactional condition appeared to be more unstable under the AZ-8 treatment, and

more subject to unpredictable and rapid change toward either improvement or deterioration. In several individual patients, the changes were not constantly in one direction, but fluctuated violently.

Initial improvement.—An initial improvement was seen in 13 patients, beginning usually on the 3rd day of treatment and lasting until the 10th day. In some patients, the improvement was marked: many of the erythema nodosum lesions disappeared, the adenitis became less tense and painful, the infiltration became less edematous and erythematous, and a general sense of well-being became apparent. The tense-ness and shininess of the ear lobes and helices improved. Chronic lep-rotic ulcers in the indurated skin of the arms, discharging enormous numbers of acid-fast bacilli, healed over for the first time for months. Slightly raised temperatures fell to normal. Corresponding with the im-provement in the general condition noticeable at the end of the first week of treatment, the individual erythema nodosum lesions became flatter and less tender, and the diffuse panniculitis diminished both in extent and in degree of induration and became less painful.

The single patient with reactional borderline leprosy was one of those who showed marked and lasting improvement in the reactional state after the third day of treatment. The lesions began to diminish in elevation and erythema, and at the end of the course they were com-pletely flat.

The remaining 10 patients experienced no initial improvement. In 6 there was a waxing and waning of the activity of the erythema nodo-sum lesions during this period, with disappearance of some lesions and reappearance of others, and development of new lesions. In 4 patients, no change was noted in the severity or clinical appearance of the lesions.

Exacerbation of the reactional state.—Exacerbation occurred in 1 patient after a week's treatment, and in 4 patients during the fourth week, of such severity that treatment with AZ-8 had to be abandoned. This exacerbation was characterized by deterioration in the general condition, elevated temperature, increase in tenseness and shininess of the helices and of the infiltrative skin lesions generally, extensive crops of erythema nodosum lesions, and increased nerve pain.

In 6 other patients there was some deterioration in the general con-dition, although not of such severity that they wished to forgo a treat-ment that held out some hope of relief.

On the 4th day after cessation of the treatment (which lasted for 50 days in 18 of the patients), 5 patients experienced sudden deterioration in their reactional state, with appearance of crops of new erythema nodosum lesions, a phenomenon that may be explicable on the supposi-tion that AZ-8 had some repressive action on the clinical manifestations of the reactional state in these patients. That the clinical state had not been permanently or incurably aggravated by the treatment is indicated

by the fact that all were controlled subsequently without undue difficulty by antireaction drugs in general use, e.g., antimony drugs or corticosteroids. Under such cover, standard doses of antileprosy drugs could be given again in cases where they had been suppressed.

SUMMARY

Twenty-three lepromatous patients under therapy, suffering from severe reactional conditions which were longstanding or recurrent in all but 6, were given recommended doses of an azulene derivative, AZ-8—1,4, dimethyl-7-isopropyl azulene.

Thirteen patients experienced temporary improvement, more or less well marked, beginning on the third day. In 6, the reactional condition pursued a variable course, and in 4 there was no change.

Five patients had such severe exacerbation of their condition that treatment with the drug had to be discontinued.

On the 4th day after the end of the full 50-day course of treatment, 5 out of the other 18 patients experienced sudden deterioration in their reactional condition.

It is concluded that the drug has an erratic and inconsistent effect on longstanding reactional states in lepromatous patients.

Addendum.—Since the present cases were reviewed a further report, by Terencio (⁸), has appeared. Good results are said to have been obtained with AZ-8 in 8 out of 10 Spanish patients suffering from lepra reaction.

RESUMEN

Veintitrés enfermos lepromatosos bajo tratamiento, que padecían de graves estados reactivos de larga duración o recurrentes en todos menos 6, recibieron dosis recomendadas de un derivado azulénico, AZ-8 1,4, dimetil-7-isopropil-azuleno.

Trece enfermos experimentaron mejoría temporal, más o menos acentuada, comenzando el tercer día. En 6, el estado reactivo prosiguió una evolución variable, y en 4 no hubo modificación.

Cinco enfermos mostraron una exacerbación tan grave de su estado que hubo que discontinuar el tratamiento con la droga.

Al 4o. día consecutivo al final de la serie completa de 50 días de tratamiento, 5 de los otros 18 enfermos experimentaron un grave deterioro de su estado reactivo.

Se deduce que la droga ejerce un efecto caprichoso e inconstante sobre los estados reactivos de larga duración en enfermos lepromatosos pigmentados intensamente.

RESUMÉ

Un dérivé de l'azulène, le AZ-8 1,4, dimethyl-7-isopropyl azulène, a été administré aux doses prescrites à 23 lépromateux en traitement. Ces malades, sauf six d'entre eux, souffraient de phénomènes réactionnels graves persistant depuis longtemps ou constamment répétés.

Treize malades ont présenté une amélioration temporaire, plus ou moins marquée, à dater du troisième jour. Chez 6 malades, les phénomènes réactionnels ont poursuivi une évolution variable, et chez 4 aucun changement n'a été noté.

Cinq malades ont présenté une aggravation tellement sévère de leur état que l'administration du médicament a dû être interrompue.

Le quatrième jour après la fin du traitement complet (qui a duré 50 jours), 5 parmi

les 18 autres malades ont présenté une aggravation des phénomènes de réaction.

En conclusion, ce médicament est doué d'une action variable et imprévisible sur les phénomènes réactionnels persistants depuis longtemps chez des malades lépromateux à peau foncée.

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