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## CHEMOTHERAPY OF LEPROSY\*

by

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Although chaulmoogra oil has been used for centuries in the treatment of leprosy, its therapeutic value has not been generally accepted (1). For this reason all new remedies which offered any hope of success have been employed in the experimental treatment of this disease. From time to time one after another of these have been heralded as specifics, only eventually to be discarded as failures.

At the National Leprosarium, Carville, Louisiana, as elsewhere, numerous experimental treatments have been investigated. The most encouraging of these, beyond any doubt, have been some of the new sulfone drugs. Three of these, promin, diasone, and promizole, have been used intensively in the treatment of leprosy. An ever-increasing number of patients has been subjected to this therapy with a steady improvement in most instances.

Promin is the sodium salt of p.p. diaminodiphenylsulfone n.n. didextrose sulfonate. Diasone is disodium formaldehyde sulfoxylate diaminodiphenyl sulfone. Promizole is 4,2'-diaminophenyl-5'-thiazole sulfone. Diaminodiphenyl sulfone, the parent chemical from which these drugs are derived, seems to be the active principle of each.

It is well known that the sulfone drugs were first assayed with satisfactory results in experimental animal tuberculosis by Feldman et al (2, 3, 4), Calloman (5), and others. They were later put to therapeutic test in human tuberculosis by Hinshaw (6, 9), Petter and Prenzlau (7, 8), and others, with conflicting findings. At present it seems that the sulfone drugs have been abandoned in clinical tuberculosis in favor of antibiotics. Whether this is a wise decision only time will tell.

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## TECHNIC OF ADMINISTRATION

In leprosy, promin treatment was initiated at the Carville Leprosarium in March, 1941 (10, 11). Oral administration was tried first but proved to be too toxic. The patients could not tolerate an adequate dose. Since then intravenous injections of promin have been favored in all cases.

Promin treatment is usually started with 1 gram daily, which dose is gradually increased in an attempt to reach the optimal dose of 5 grams daily. In the majority of patients this dose is attained. In some patients, who develop repeated toxic reactions, the maximum daily dose may not exceed 2 grams. Experience has shown the wisdom of discontinuing treatment for one week following each two weeks of daily intravenous injections of promin. This routine technic has resulted in fewer and milder types of toxic reactions. During the week of rest, sufficient time is usually afforded the patient's hematopoietic system to restore the blood cells lost through the hemolytic action of this drug. It is seldom necessary to administer iron and liver extract as adjuvants for anemia.

Urinalysis and red and white blood cell counts and hemoglobin estimations are performed on each patient every three weeks. The blood concentration of promin following each intravenous administration rises rapidly but is transitory. The drug is rapidly eliminated in the urine, and, usually, only a trace or none remains in the blood stream at the end of 24 hours. Occasionally, however, in patients with severe renal impairment, after a prolonged course of treatment, there is apt to be an accumulation of promin in the blood. In such cases, high blood levels, reaching 20 to 30 mgm. per cent in 24 hours, have been found. In such cases the dosage must be materially reduced.

Diasone therapy was initiated in this hospital in July, 1943 (12, 14). Muir's experience with diasone (13) has been somewhat similar to ours but was of a shorter duration. Diasone has the advantage over promin of being less toxic by oral administration. Treatment should be started with small doses, which are gradually increased as the patient builds up a tolerance for the drug. At present, treatment is started with one 5-grain capsule by mouth daily. Provided no toxic reactions are observed in 2 weeks, the dose is increased to two 5-grain capsules a day. After a few more weeks, in the majority of patients, the optimal dose of 5 grains three times a day is tolerated. Rest periods of two weeks are advisable every two months. Periodic laboratory examinations of blood and urine are necessary, as with patients taking promin. Occasionally it is found necessary to administer iron and liver extract to counteract secondary anemia.

Blood levels of diasone have been found to be low, since the drug is rapidly excreted in the urine. An initial rise of several mgm. per cent declines to from 1 mgm. per cent to a trace 12 hours after the evening dose.

Promizole as a treatment of leprosy was started at the Carville Leprosarium in March, 1945 (15). It is administered by mouth in tablets or capsules containing 0.5 gram each. At first 0.5 to 1 gram is given three times a day. After 1 to 2 weeks this dose is gradually increased to individual tolerance. An optimal dose of 6 to 8 grams a day is seldom exceeded. Toxic manifestations are rare and usually mild but, when they occur, are similar to those of promin and diasone therapy (10, 12). Frequent clinical and laboratory examinations are likewise necessary to detect any untoward manifestations early.

With large daily doses of promizole it is found that the blood level declines rapidly and reaches 1 to 2 mgm. per cent 12 hours after the last dose.

None of the sulfone drugs produce crystalluria. No evidence of renal damage has been observed under the carefully controlled technic of medication employed in this institution. Early in our experimental study with diasone, when a large initial dose of 15 grains daily was used, a few cases of hematuria were encountered. Even in these patients no crystals were recovered from the urine after careful search, and the causative factor of the hematuria was not determined.

#### THERAPEUTIC EFFECTS

With but few exceptions, only lepromatous leprosy and mostly far advanced cases have been subjected to sulfone therapy. While no claim is made that these drugs are specific remedies, they have proved therapeutically more effective in leprosy than any previous treatment tried at the Carville Leprosarium. Unfortunately they work slowly. Definite objective improvement, as a rule, seldom becomes manifested before 6 months of treatment. Thereafter, improvement is progressive with few, if any, relapses. The disease seldom, if ever, appears to get worse under treatment. The percentage of patients improved is in direct proportion to the duration and the intensity of treatment. It is the writer's impression that the progress of improvement is very similar with each of the three drugs. The diamino-diphenyl sulfone parent radical, common to all, appears to be the active principle. That the patients in the promin group are as a whole in the best condition at present can probably be attributed entirely to their being under treatment for the longest period of time.

Experience has shown that the relation of improvement to duration of treatment can be approximately estimated. After 6 months of treatment almost 25 per cent of the patients show some improvement. After 1 year this percentage is increased to 60, after 2 years to 75, after 3 years to almost 100. The extent and stage of the disease does not suppress the action of the sulfone. Even far advanced lepromatous disease is checked and improves under treatment. The extent of improvement usually varies proportionately with the size of the dosage tolerated by the individual patient.

Only objective improvement has been considered in evaluating the therapeutic action of the sulfones. Clinical objective improvement is substantiated by photographic and laboratory evidence.

Clinical improvement in lepromatous cases is manifested in various ways. Small nodular lesions slowly shrink and flatten to complete absorption. Finally only a pigmented spot usually remains. Larger and deeper nodular lesions disintegrate more slowly with subsequent scar formation. Infiltrative plaques gradually subside with diminution of inflammatory swelling and edema of dermal tissues. Leprous ulcerations of extremities gradually form healthy granulations and heal through cicatrix formation. Trophic plantar ulcers become disinfected, granulate, and gradually close with residual callosities.

Occasionally regrowth of hair may follow resolution of lepromatous lesions. This has been found to occur in eyebrows, beard, and arms and legs. Mucosal lesions appear to respond more rapidly than cutaneous lesions. Oral nodules and infiltrations usually subside and disappear after a few months. Oral ulcerations also heal within a few months to a year. Nasal obstruction is relieved through subsidence of the inflammatory mucosal lesions of leprous rhinitis. Epistaxis is checked by the healing of nasal mucosal ulcerations. Improvement in leprous laryngitis occurs frequently, with restoration of the patient's voice and relief of dyspnea. Emergency tracheotomies generally become unnecessary.

Sulfone therapy appears capable of checking the progress of conjunctival, corneal, and iridocyclitic leprous infiltration. There is occasional improvement of impaired vision.

#### ACUTE LEPROUS REACTIONS

Attacks of acute leprous reactions with erythema nodosum or erysipeloid dermatitis are not commonly aborted by sulfone therapy. Patients experiencing such episodes previously may have recurrences during the course of treatment. However, the frequency as well as the severity of subsequent attacks is lessened by this

treatment. In only a few cases, severe attacks have occurred despite treatment. In some of these instances it was found best temporarily to discontinue the administration of the sulfone drugs.

Attacks of acute iridocyclitis may occasionally occur during the course of sulfone therapy. These are generally mild and subside upon continuation or intensification of treatment. Episodes of acute leprous neuritis are also not prevented or aborted by sulfone therapy. However, it is believed that these drugs are not responsible for the initiation of these acute inflammatory reactions in leprous nerves.

#### BACTERIOSCOPY

Another feature in the improvement during sulfone therapy is the reversion of skin and nasal smears from bacteriologically positive to negative. Statistically, it has been found that the percentage of bacterioscopically negative smears among treated patients is in direct proportion to the duration of treatment. During the first year of treatment, practically all lepromatous cases remain bacilliferous. During subsequent years of treatment, an ever-increasing proportion of patients revert from positive to negative in the routine monthly skin and nasal smears. After 4 years of continuous intensive treatment the incidence of negative reports exceeds 50 per cent. This strongly suggests that the sulfone drugs have some bacteriostatic properties against Hansen's bacillus.

A study of the histopathology of lesions before and after prolonged promin treatment has been reported by Fite (16). His findings indicate that promin appears to eliminate bacillary infection from the blood stream and the small blood vessels, thereby preventing the formation of new lesions. Improvement under promin does not seem to be accompanied by characteristic cellular changes. The histopathologic changes which do occur are predominantly of an atrophic nature, with gradual lessening of the number of acid-fast organisms present in the lesion to the point of final disappearance.

#### STATISTICS

At present in the Carville Leprosarium, 163 patients are on promin therapy, 122 on diasone, and 25 on promizole. In the promin group 8 patients have been under treatment for 5 years, 41 for 4 years, 18 for 3 years, 38 for 2 years, 30 for 1 year, and 28 for less than 1 year. In the diasone group 4 patients have taken treatment for 3 years, 37 for 2 years, 28 for 1 year, and 52 for less than 1 year. In the promizole group 7 patients have been under treatment for more than 1 year, 8 for more than 6 months, and 4 for less than 6 months.

Nineteen promin-treated patients have been discharged as disease arrested following 12 consecutive months of negative bacterioscopy. Of this number 3 were under treatment for 1½ to 2 years, 3 from 2 to 3 years, 6 from 3 to 4 years, and 7 from 4 to 5 years. There have been no known relapses and 5 of these patients have chosen to remain under observation in the institution. The period of observation following arrest of the disease has varied from a few months to 2½ years. Two diasone-treated patients were discharged with arrested disease. Each had taken treatment for a period of 1½ years. Both have since remained under close observation for 4 months and 1½ years respectively, without recurrence of the disease. It is too early to expect arrested cases in the promizole-treated group.

During the last fiscal year the number of patients discharged as arrested cases has more than doubled the average for the 10 years prior to the institution of sulfone therapy and the number of deaths was less than half the average for the previous years. This good record can be attributed entirely to the beneficial effects of sulfone therapy. The institution's population has remained stationary during the period under consideration.

#### ANTIBIOTICS

Penicillin has been used in large doses in the treatment of leprosy and has proved unsuccessful (17). At present streptomycin is being tried as a possible chemotherapy for leprosy. Ten patients are being given a maximum sustained dosage of 250,000 "S" units every 3 hours by intramuscular injections. This total of 2,000,000 "S" units, or 2 grams, daily has been continued for three months. The results, not yet conclusive, seem encouraging and will be reported at a later date. It is possible that a combination of streptomycin and one of the sulfone drugs may become the treatment of choice for leprosy in the near future.

#### CONCLUSIONS

(1) In the chemotherapy of leprosy with the sulfone drugs, promin, diasone, and promizole, objective clinical improvements are produced which are sustained and cannot be attributed to spontaneous remissions in the disease.

(2) These objective improvements, although slow in their development, are progressive during the course of treatment.

(3) They are substantiated by the photographic changes which occur in the lesions.



(4) Laboratory examinations indicate that the sulfone drugs have a bacteriostatic action in leprosy.

(5) Since the sulfone drugs are slowly-acting chemotherapeutic agents, further research should be continued in the hope of discovering more powerful bactericidal agents.

(6) Streptomycin is an antibiotic deserving further investigation as a possible chemotherapeutic agent for leprosy.

(7) Until faster-acting remedies are discovered, the sulfone drugs must be considered the optimal treatment of leprosy.

(8) Their further investigation in all leprosaria throughout the world is recommended.

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