REPRINTED ARTICLE

[EDITOR'S NOTE: The sulfone treatment of leprosy has apparently led to greater success than any other therapy for this disease in its age-long history. Since the first extended report on sulfone therapy is not widely accessible to subscribers to the INTERNATIONAL JOURNAL OF LEPROSY it is here reprinted for its general interest.]

The Promin Treatment of Leprosy

A Progress Report[1]

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Promin, the sodium salt of p. p. diaminodiphenylsulfone n. n. didextrose sulfonate, has been used in experimental tuberculosis in guinea pigs with remarkable success (1). Its clinical trial in human tuberculosis as a chemotherapeutic agent has met with at least promising results (2). Its experimental use in the treatment of leprosy was commenced by the writers over 2 years ago, and at present it is felt that promin is a therapeutic agent worthy of further trial in human leprosy. The writers have had no experience with the drug in murine leprosy, but in this type of the disease the reports are suggestive of slight action (3).

In our experience promin is the best of all the sulfonamide derivatives, including sulfanilamide, sulfathiazole, sulfapyridine, and sulfadiazine, which have been used in the treatment of leprosy at the National Leprosarium (4). It can be regarded as the most encouraging experimental treatment ever undertaken at the National Leprosarium. The writers are not in a position at this time to state that it possesses any specific action upon Hansen's bacillus. They consider it an advance in the right direction in the chemotheraphy of leprosy and hope that further synthesis of the sulfa chemicals will produce a product which has specific properties against *M. leprae* and *M. tuberculosis.*

Our experimental study was made possible through the cooperation of Parke Davis & Co., the manufacturers of promin, which was generously supplied gratis for this experiment through Dr. E. A. Sharp, the director of the Department of Clinical Investigation of this firm.

TECHNIC

Promin can be given orally or intravenously. By oral administration it is more toxic, and much larger doses are tolerated

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by the intravenous route. In our preliminary studies promin was given by mouth to a group of 10 patients. Small doses of ½ to 1 gm. were tolerated for such short periods that therapeutic effects seemed unlikely by this method of administration. Severe reactions, particularly hemolysis, were so easily provoked that this mode of medication was soon abandoned. Since then the intravenous injection has been favored in all cases. The great majority of patients under treatment have received from 1 to 5 gm. daily for 6 days a week, Sunday excepted. Most of the patients were given the 5-gm. dose, and the course of treatment was continuous for months with only short intervals of rest of 1 to 2 weeks three times a year. In the case reports, in calculating the average daily dose, these rest periods and Sundays are included.

Studies of the promin concentration in the blood showed a rapid decline. It was found that only traces remained 6 to 8 hours following the intravenous administration of 5 gm. of promin.

TOXIC MANIFESTATIONS

The intravenous administration of promin is not free from toxic reactions. The most important of these is a slow destruction of the erythrocytes. This effect is generally delayed for several weeks, but one must be constantly on the alert for its development. It is our practice to do complete blood counts routinely every 2 weeks on every patient on this treatment.

In the writers' experience, anemia occurs in 46 per cent of cases after 6 weeks of intravenous promin therapy. The longer the continuous course of treatment, the greater the number of anemic patients. It was observed that during the complete course of treatment the erythrocytes fell to 3.5 million or less in 71 per cent of cases and in 9 per cent they fell below 3 million. In the great majority of these cases antianemic therapy, with or without cessations of promin, was successful in raising the red blood cells and hemoglobin to their former levels.

Satisfactory maintenance of blood levels can be attained in several ways. A fall of the red blood cells below 4 million is an indication to start the patient on inorganic iron, ferrous sulfate, or ferrous carbonate, in adequate doses. This usually restores the red blood cell count and hemoglobin level, as occurred in 66 per cent of our cases. If the erythrocytes continue to decrease, an oral liver and iron preparation is substituted for the iron. This proved adequate in readjusting the erythrocytes and hemoglobin in 60 per cent of cases not responding to iron alone. A certain percentage of patients do not respond to these simple measures. In such instances and whenever the red blood cells decline below 3 million, promin is discontinued temporarily and liver extract is administered parenterally in addition to iron orally. This treatment is continued until the erythrocytes rise above 3.5 million, when it is considered safe to resume promin therapy at the rate of 2 gm. a day, provided the liver and iron are continued.

According to Higgins ([5]) promin in guinea pigs exerts a direct toxic effect on the erythrocytes, leading to their destruction and removal from the blood by the spleen. He found that promin did not permanently damage the bone marrow and regeneration of erythrocytes proceeded during continuous administration of the drug.

The writers have observed that in some cases the institution of promin therapy actually resulted in an increase in the red blood cell count and the hemoglobin percentage. It is believed that in such cases the healing of secondary infections results in a general improvement in the patient's health, one of the manifestations of which is the lessening of secondary anemia.

Besides a decrease in the red blood cells, leucopenia has been encountered. It occurred in 3 per cent of the cases under treatment. Severe agranulocytosis did not develop, but it was thought best to discontinue promin promptly whenever the white blood cells fell below 3,000. In one case promin treatment was abandoned because the response to injections of pentnucleotide and liver extract was unsatisfactory.

A routine bimonthly urinalysis is another precautionary measure instituted in this experimental study, since other sulfonamides are known to cause renal impairment. So

far, no evidence of kidney irritation or damage has been demonstrated by the routine urinalyses, which are supplemented by occasional renal function tests whenever deemed indicated. Toomey and Tokacs ([6]) were not successful in attempts to produce urinary concretion in monkeys by intravenous injections of promin doses six times as large as those recommended for human beings.

After hemolysis, the most important toxic reaction was the development of an allergic dermatitis. This generally manifested itself as a diffuse maculopapular eruption which was accompanied by intense itching. Dermatitis medicamentosa is, of course, a cause for temporarily discontinuing promin therapy. In the majority of these allergic patients, desensitization is feasible. After the eruption has completely disappeared, promin is resumed in minute doses, 0.1 gm., intravenously. By gradually increasing the dose over a period of approximately one month, it is possible to arrive at therapeutic doses of 2 gm. daily without further allergic reactions. In some cases full doses of 5 gm. are eventually reached without a recurrence of dermatitis.

Allergic dermatitis occurred in 16 per cent of the patients under study. Two-thirds of these have been desensitized at present. In only 3 per cent of cases the procedure proved entirely unsuccessful; the others are in the process of desensitization.

Another manifestation is allergic rhinitis, which developed in one patient. After several months the sneezing episodes following each injection of promin ceased.

Other untoward reactions, headaches and nausea, are generally mild and ephemeral. Nausea occurred in 35 per cent of cases. It is transitory in nature and can be prevented by injecting the drug more slowly. Vomiting followed nausea in only 7 per cent of cases. It also responds to slower injection, up to 1 minute being required to administer 5 gm. of promin intravenously. Several patients complained of headaches, which were never severe.

An increase in erythema of leprous plaques was noted in 3 per cent of the cases. This accompanied the first few weeks of treatment and gradually subsided. Its cause is unknown. Acute lepra reactions with fever and the appearance of erythema nodosum occurs less frequently with promin than with most previous experimental treatments or than with the routine chaulmoogra oil injections. It was the cause of discontinuing promin therapy in only four cases.

An exacerbation of an iridocyclitis occurred in 10 per cent of cases. In all of them the patient had experienced frequent previous attacks of iridocyclitis. This drug seems temporarily to increase the severity of the ocular inflammation, which is generally followed by improvement. In only one patient the exacerbation of iridocyclitis initiated by promin persisted longer than 1 month.

A generalized lymphadenitis was another unusual toxic manifestation which occurred in one patient. Reduction of the dose of promin to 1 gm. resulted in the subsidence of the glandular enlargement.

CLINICAL MATERIAL

No attempt was made to select minimal or moderately advanced cases with favorable prognosis. Thus only a few cases of neural and maculoanesthetic types are included in the study. All patients treated were bacterioscopically positive at onset and many had never had a negative bacteriologic report during the entire previous period of hospitalization. Many patients volunteering for treatment had far advanced lepromatous and mixed types of leprosy with poor prognosis. The disease in the majority of cases was showing a definite trend toward aggravation before the institution of promin therapy. Several cases were selected because of certain complications which it was thought might be favorably influenced by the promin. Among these important complications were: Leprous keratitis and iridocyclitis, with pending loss of vision in some cases; leprous rhinitis with ulcerations, repeated epistaxis and partial obstruction of nares; leprous laryngitis with threatening suffocation; chronic leprous ulcerations; and lepromatous lesions and ulcers of the tongue, palate, gums, and lips, which usually respond poorly to other forms of treatment. The

effects of promin in these complications of leprosy have, for the most part, been good.

Patients with eye, nose, and throat complications were examined before and during the course of treatment in the eye, ear, nose, and throat clinic, and those with oral lesions were examined in like manner in the dental clinic.

The eye, ear, nose, and throat specialist (J. F. D.) reports that many patients under promin therapy showed a marked improvement in nasal breathing. The initial examination in these patients reveals ulcerations of the nasal mucous membrane and excessive mucous secretion, which on drying and crusting produces blockage of the nasal passages. There is also a tendency to frequent epistaxis. After a course of promin it is observed that the ulcerations, which are probably due to secondary infection, heal, the excessive secretion and crust formation subside, and nasal bleeding ceases.

Another observation is that promin seems to benefit eye complications of leprosy. It is noted that patients on promin therapy do not have so many attacks of acute iridocyclitis as formerly. Two patients have shown by slit lamp examination that leprous punctate keratitis has disappeared to a considerable extent.

Objective improvement in vision has been marked in only one patient. This patient started with only light perception and projection in one eye, the other being totally blind. Shortly after the institution of promin parenterally, the acute iridocyclitis and edema of the cornea gradually improved. This continued until on the last examination it was found that he had recovered 20/100 vision in his good eye.

Many patients with advanced lepromatous and mixed leprosy show evidence of leprous laryngitis. The symptoms are huskiness of voice, vocal weakness, dryness of the throat with unproductive cough, and finally attacks of respiratory difficulty. Six patients with advanced leprous laryngitis were started on promin intravenously, and all of them improved, especially in the quality of their voices and the restoration of comfortable respiration. It is felt that two of these patients escaped a proposed emergency tracheotomy because of the beneficial relief attributable to promin therapy.

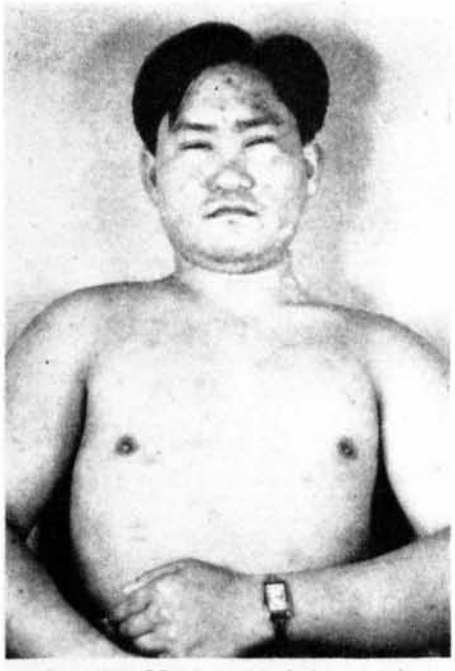
In the dental clinic it was noted that in several patients leprous lesions of lips, tongue, gums, and hard and soft palate have diminished and in four patients completely disappeared after prolonged treatment with promin. Some mucosal ulcerations of the hard and soft palate and of the lips have healed under the influence of promin.

CASE REPORTS

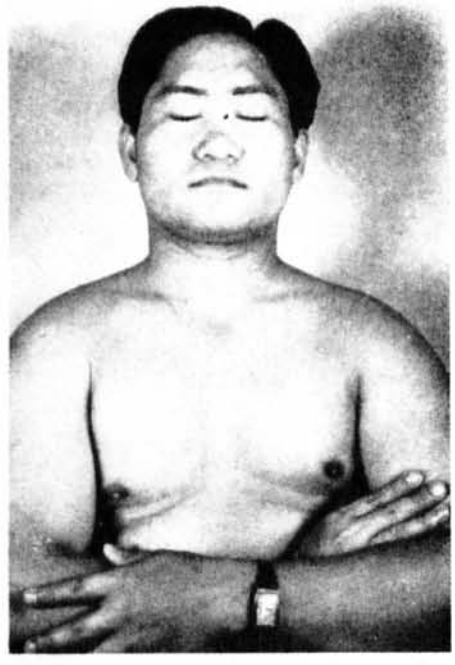
A brief summary of the progress of patients having taken at least 12 months of promin treatment is given in the following case reports:

Case 869. White male, 28 years of age, is a moderately advanced lepromatous (nodular) case of 12 years' duration. There was little previous improvement during 9 years of hospitalization. A total of 2,030 gm. of promin was given intravenously during 26 months. The average daily dose, including rest periods, was 2.6 gm. After 6 months of treatment there was a gradual disappearance of discrete nodules of face and torso. At present the patient appears entirely free of leprous lesions. The monthly skin smears became bacteriologically negative after 2 years of treatment. An occasional acid-fast bacillus was found in one subsequent skin smear. Photographic confirmation of improvement is evident.

Case 864. A 36-year-old white male with far-advanced lepromatous (nodular) leprosy of 12 years' duration had shown no recent advance in the disease prior to promin therapy. He was given 1,375 gm. intravenously during a period of 26 months. The daily dose averaged 1.7 gm. including rest periods. These rest periods and hematopoietic drugs were necessary to combat toxic hemolytic anemia. The erythrocytes varied from 3.02 to 4.67 million during the course of treatment. It was observed that facial nodules definitely retrogressed in size and prominence. This improvement started gradually after about a year's treatment and has been progressive. A troublesome nasal obstruction secondary to lep-



Case 869. March 1, 1941, before promin treatment.



Case 869. April 2, 1943, 2 years after promin treatment was started.

Case 1206. May 1, 1941, before promin treatment.

Case 1206. May 2, 1943, 2 years after promin treatment was started.

rous rhinitis has apparently completely cleared up. General improvement is shown in the patient's ability to play baseball this season for the first time in 3 years.

Case 714. A white male, 23 years of age, with far-advanced mixed type of leprosy showed a progressive aggravation of the disease during the 13 years prior to treatment with promin. The course of treatment, of 24 months' duration, has consisted of 1,819 gm., averaging 2.5 gm. daily including rest periods. Several chronic ulcers of the legs have healed, as well as a few small ulcers of the face and hands. Nasal obstruction complicating a leprous rhinitis has been relieved. The patient has greater energy and stamina, but there is no definite objective improvement in leprous lesions.

Case 1206. White male, 59 years old, has a far-advanced mixed type of leprosy of 9 years' duration. He was getting worse before the onset of the present treatment. A total of 1,814 gm. of promin was injected intravenously during a period of 24 months, an average of 2.8 gm. daily including rest periods. There were very extensive chronic ulcerations of the extremities. These have all healed with the exception of two leg ulcers which are small at present. Nasal obstruction and bleeding, symptoms of leprous rhinitis, are relieved. Previous to promin therapy this patient was confined to the infirmary because of general weakness and laryngeal leprosy with threatened suffocation. An emergency tracheotomy seemed indicated. He is now ambulatory with laryngeal condition improved. Improvement in this elderly patient is definite.

Case 661. A white female, 27 years old, with moderately advanced lepromatous (nodular) leprosy of 15 years' duration was showing no evidence of improvement at the time of onset of the present treatment. Promin intravenously was given for 19 months, totaling 1,265 gm. Including rest periods, the average daily dose was 2.2 gm. Definite objective improvement is noted. Nodules on arms and legs are smaller and flatter. A few nodules have disappeared, leaving a brownish pigmentation. Improvement has been consistent to date.

Case 1229. A colored male, 43 years of age, was under previous routine treatment for 6 years without any definite improvement. The disease is a moderately advanced mixed type of leprosy. Present treatment totals 717 gm. of promin given during the course of 18 months for an average daily dose of 1.3 gm., counting the rest periods. Promin was at first administered orally, but toxic reactions prevented its continuation by this route. The greater part of the drug was administered intravenously. The first bacteriologically negative skin smear was recorded after 1 year of treatment. Because the patient disliked daily injections, sulfathiazole was finally substituted for promin. The manifestations of leprosy have gradually receded. There has been one skin smear showing an occasional acid-fast bacillus since the first negative report, but subsequent skin smears have again reverted to negative. It is felt that promin is responsible for the definite objective improvement in this case.

Case 1366. White male, 38 years of age, has suffered from mixed type of leprosy of a moderately advanced stage for 13 years. The disease had recently become worse. The course of intravenous promin therapy was of 19 months' duration with short intervals of rest. A total of 2,011 gm. was given for an average of 3.5 gm. daily. This has resulted in a slight decrease in the size and elevation of the nodules of the face, chest, and arms. There has also supervened a marked increase in physical capacity for work. Improvement is slight in this patient.

Case 1294. White male, 34 years of age, has had leprosy for 17 years. The disease was moderately advanced and predominantly lepromatous in type and considered stationary before starting treatment with promin intravenously. This treatment was administered for 17 months, during which time 1,523 gm. were injected, an average daily dose of 3 gm. There resulted a healing of leprous ulcers of the lips, mouth, and nose. Eight ulcerations of the legs, the largest 4 cm. in diameter and 2 mm. in depth, are also completely healed at present. Leprous infiltration of the face has diminished. During a rest period in December 1941 an erysipeloid reaction of the face developed and during a rest period in September 1942

a severe cystitis developed. Both conditions were relieved upon resumption of promin and have not recurred during the course of treatment. At one time granulocytopenia developed and the number of leukocytes dropped to a low of 3,000 with a polymorphonuclear count of 18 per cent. This condition responded well to the temporary discontinuance of the drug and the injection of liver extract. The neutrophiles have remained within normal limits since then, in spite of resumption of full doses of promin. Improvement in this case seems objectively definite.

Case 1413. White male, 57 years old, has had leprosy for 7 years. Prior to institution of promin therapy the disease had an unfavorable course and reached a moderately advanced stage of the mixed type. Promin was given irregularly because of poor veins. Orally it was found to produce too severe toxic reactions. For many months the patient received it by daily intramuscular injections in the buttock, which he tolerated in spite of the pain. In all 519 gm. were administered during a period of 17 months, averaging about 1 gm. daily. Poor veins and painful intramuscular injections were the cause for substituting sulfathiazole orally for promin. Under these treatments, skin infiltrations subsided and large ulcers of the lower extremities healed partially. The patient has finally succeeded in obtaining two successive negative bacteriologic skin smears at monthly intervals. The contribution of promin toward these negative tests, which occurred 5 months after the treatment was changed to sulfathiazole, is questionable. For this reason this case is tabulated as stationary in the following table.

Case 1078. White male, 41 years of age, has moderately advanced lepromatous (nodular) leprosy of 9 years' duration. His condition had been stationary for a year previous to onset of promin therapy. This treatment consisted of 1,121 gm. of promin given intravenously for a period of 16 months. In spite of several interruptions, because of multiple operations for a squamous carcinoma of the nose, the daily dose averaged 2.3 gm. It was observed that numerous nodules of the abdomen and arms became flattened or disappeared entirely, leaving small scars. During a prolonged period of cessation of treatment a few new nodules developed on the abdomen. These receded upon resumption of treatment. The patient at present has again been transferred to another hospital for further plastic operations on his nose. It is felt that improvement in this case is objective and definite, although not continuous due to frequent interruptions in treatment.

Case 953. White male, 29 years of age, has had leprosy for 10 years. The disease progressed unfavorably prior to treatment. It is lepromatous (nodular) in type and moderately advanced. Treatment to the present has comprised the intravenous injection of 1,578 gm. of promin during a 16 months' period for an average of 3.2 gm. a day. Objective improvement is manifested by subsidence of lepromatous plaques of the face and a decrease in infiltration of the legs with some new growth of hair. The patient is encouraged over the results thus far obtained.

Case 1032. White male, 28 years of age, has had leprosy for 10 years. The disease has grown progressively worse each year. At the start of promin therapy it had reached a far-advanced stage and was of mixed type. During the course of 16 months of treatment he was given 1,505 gm. of promin intravenously for an average of 3.1 gm. a day. The principal reason for starting treatment in this patient was the seriousness of ocular complications, leprous keratitis, and iridocyclitis, which were destroying his sight. Improvement in vision was definite. At the start of treatment the patient had to be led into the room for his injections. At present he reads 20/200 and Jaeger IV. Nasal discharge and epistaxis due to leprous rhinitis also ceased.

Case 1293. White female, 34 years of age, has had leprosy for 17 years. At the time that promin therapy was started the disease was progressing unfavorably. Her case was classed as a moderately advanced lepromatous (nodular) type. At present she has had 15 months of treatment totaling 335 gm. and averaging only 0.7 gm. daily. The course and dosage were restricted because of allergic dermatitis which neces-

sitated desensitization by gradually increasing doses commencing at 0.1 gm. intravenously. A tendency to anemia which responded only fairly well to liver, ventrex, and inorganic iron also resulted in frequent interruptions in the course of treatment. It is observed that some pigmented infiltrated lesions of the arms and thighs are subsiding under the influence of treatment. This improvement, however, has been gradual and is as yet slight, so that this case is recorded as still stationary.

Case 1195. White male, 33 years of age, has had leprosy 12 years. The disease has shown no tendency to improve, and was a moderately advanced lepromatous (nodular) type at the start of the promin treatment. This therapy, started 14 months ago, amounts to 1,072 gm., the average daily dose being 2.5 gm. The manifestation of leprosy in this patient is a diffuse infiltration of the skin of the entire body. Under promin therapy there has occurred a gradual but not a pronounced fading of these lesions. His condition is classed as stationary until and unless more marked improvement is noted.

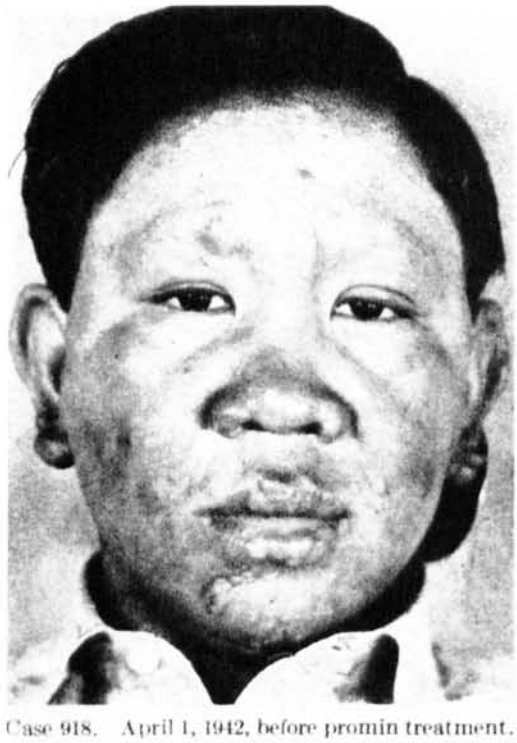
Case 575. White male, 37 years of age, has had leprosy for 18 years. The disease is a far-advanced mixed type with total blindness. A threatened respiratory obstruction from advancing leprous laryngitis was the reason for starting promin therapy in this patient. Intravenous treatment so far has consisted of 1,251 gm. of promin during a 12 months' period, which averaged 3.2 gm. a day. The laryngeal condition has improved. A nasal mucosal leprosy which prevented free nasal breathing also responded favorably. Five leprous ulcerations of the extremities have healed. Leprotic skin infiltration has subsided and skin smears have become bacteriologically negative for the last 3 consecutive months. Improvement has been unmistakable.

Case 1033. Chinese male, 25 years of age, has moderately advanced lepromatous leprosy of 8 years' duration. At present he has received 811 gm. of promin intravenously during 13 months, the average daily dose being 2.3 gm. Close examination shows no demonstrable effect of promin on the leprosy for either better or worse.

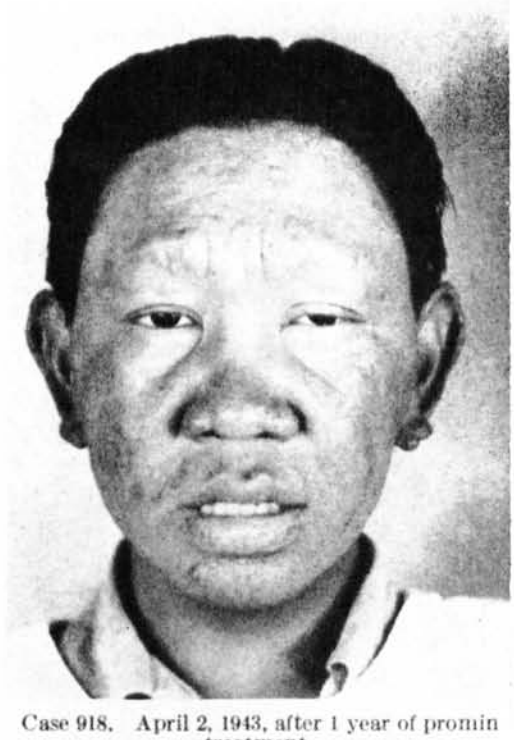
Case 576. White male, 21 years of age, has suffered from leprosy for 15 years. The disease had become far advanced and of the mixed type before promin therapy was tried. This patient also had severe chronic nephritis. Promin was administered intravenously in moderate doses for 13 months, averaging about 1 gm. daily and totaling 391 gm. A marked leprous iridocyclitis subsided but there was no improvement of leprous keratitis noted. Visual acuity did not improve but frequent nocturia was lessened. Nitrogen retention was not materially altered but dropped 20 points since the last resumption of promin 6 weeks ago. This patient's condition is still serious and at present is considered worse than at the start of treatment.

Case 689. White male, 49 years of age, who has had leprosy 18 years, was a far-advanced mixed type before starting on promin. During 13 months 1,325 gm. were administered intravenously for an average daily dose of 3.3 gm., including the rest periods. Rapidly failing vision due to leprous keratitis and iridocyclitis was the reason for trying promin. Iridocyclitis subsided but the keratitis remained the same. Nasal obstruction due to a leprous rhinitis is greatly relieved. Multiple ulcers of the legs have healed under the influence of promin. Two periods of interruption of treatment were necessary for excision of a squamous cell carcinoma of lower lip and a subsequent plastic repair. Improvement in this case is regarded as definite, although most of it may be attributed to clearing up of secondary infections.

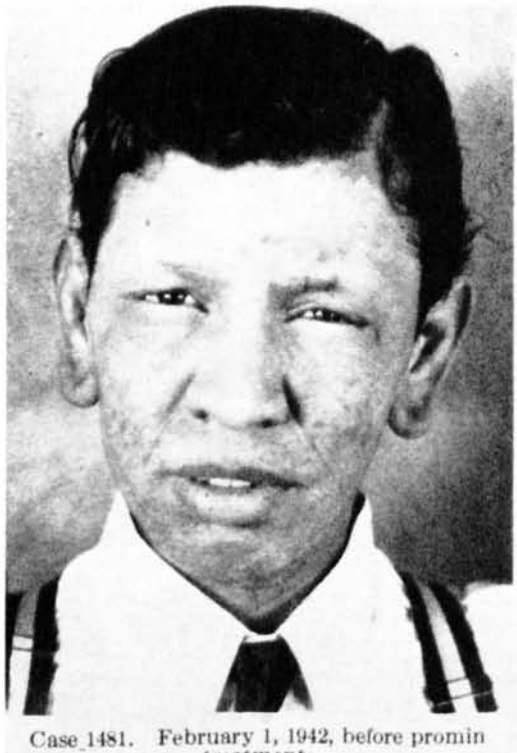
Case 1148. White male, 39 years of age, has had leprosy for 10 years. The disease was becoming worse and was of a moderately advanced mixed type at onset of promin therapy. Course of treatment consisted of 1,126 gm. of promin intravenously during a period of 12 months, the average daily dose being 3.1 gm. including days of rest. Leprous laryngitis was the reason for instituting treatment in this case. This manifested itself by hoarseness and a tendency to aphonia and dyspnoea. These symptoms were favorably influenced by promin. Scleroderma of lower legs diminished, and ulcers healed. Nodules on the legs became smaller.



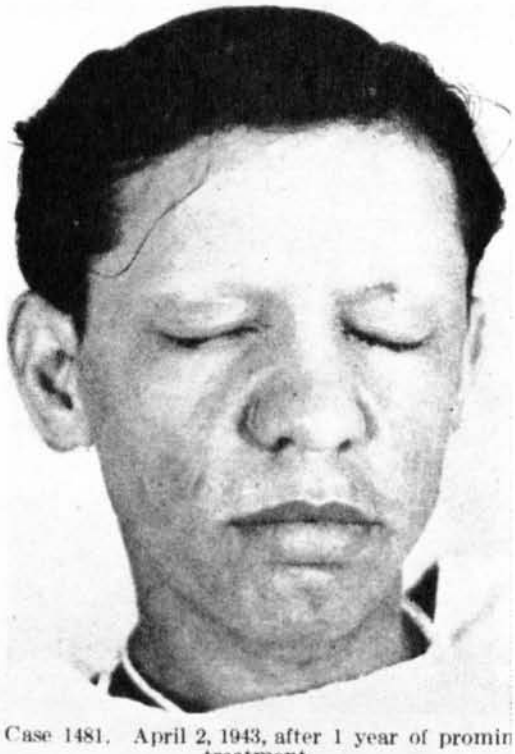
Case 918. April 1, 1942, before promin treatment.



Case 918. April 2, 1943, after 1 year of promin treatment.



Case 1481. February 1, 1942, before promin treatment.



Case 1481. April 2, 1943, after 1 year of promin treatment.

Case 1196. White male, 29 years of age, who has had leprosy 8 years had shown no definite change previous to promin treatment. The disease was moderately advanced and lepromatous (nodular) in type. He received a total of 856 gm. of promin intravenously during 12 months, an average daily dose of 2.3 gm. Improvement is manifested in subsidence of skin infiltration and nodules of ear lobes. Objective improvement is reflected in the report of the patient's first negative skin test after 11 months on promin therapy.

Case 918. Filipino male, 19 years of age, has had leprosy for 12 years. The disease is moderately advanced and of mixed type. At onset of promin therapy prognosis seemed poor, as the disease was progressing unfavorably. A total of 889 gm. of promin was administered intravenously during 12 months, which is an average daily dose of 2.4 gm. A decrease in the amount of infiltration and nodulation of the face and body has become evident. There is also a moderate lessening of scleroderma of the legs. In spite of this improvement, the patient has suffered several acute lepra reactions with erythema nodosum and has lost 5 pounds in weight.

Case 1399. White male, 20 years of age, has had leprosy for 4 years. The disease is maculoanesthetic in type and of a moderately advanced stage. Promin therapy was commenced 12 months ago. At first it was given orally, but this method of administration had to be discontinued because of a gastrointestinal disturbance and the development of hemolysis. The greater part of the 848 gm. of promin was given intravenously, an average of 2.2 gm. daily including rest periods. Macules of the body have faded to some extent. Nasal obstruction was markedly alleviated. In this case in addititon to parenteral therapy a 5-per cent solution of promin was used as a nasal spray. Skin smears are showing a smaller number of acid-fast bacilli, and the last nasal smear is reported negative.

The following table is a summation of the results of intravenous promin therapy in the patients whose case histories are reported here, each of whom has taken at least 12 months of treatment.

Not included in these case reports or in Table 1 are 46 additional patients who have taken a shorter course of promin intravenously. Some of them are beginning to show signs of improvement, and a few have reverted from a positive to a negative bacterioscopy. The duration of treatment in this more recent group of patients varies from 2 to 11 months and averages 8 months. The preliminary results of intravenous promin therapy in this group are briefly indicated in Table 2. Also shown in this table are the number of patients in whom bacteriologic tests became negative and those in whom treatment was discontinued for one reason or another.

In these more recently treated cases it can be seen that an attempt was made to select a more favorable and less advanced type of disease.

There were 16 patients altogether in whom treatment was discontinued for various reasons. This number includes a few patients taking less than 2 months' treatment, who are not otherwise included in

TABLE 1

Type	Number	Improved	Stationary	Worse	Bacteriologic reversion from positive to negative
Mixed, far advanced	6	3	2	1	1
Mixed, moderately advanced	5	4	1	0	1
Lepromatous, far advanced	1	1	0	0	0
Lepromatous, moderately advanced	9	6	3	0	3
Neural, moderately advanced	1	1	0	0	0
Total	22	15	6	1	5

TABLE 2

Type	Number	Objective improvement	Stationary	Worse	Bacterioscopy negative	Treatment discontinued
Mixed, far advanced	4	1	3	0	0	2
Mixed, moderately advanced	14	6	6	2	1	6
Lepromatous, far advanced	5	3	2	0	1	0
Lepromatous, moderately advanced	13	8	4	1	2	2
Lepromatous, minimal	4	3	1	0	1	1
Neural, moderately advanced	5	4	1	0	2	0
Neural, minimal	1	1	0	0	0	0
Total	46	26	17	3	7	11

this report. The reasons for discontinuing treatment were as follows: Refusal of patient to cooperate, 5; repeated acute lepra reactions with erythema nodosum, 4; patients absconding (improved nodular cases), 2; exfoliative dermatitis, 1; leucopenia, 1; previous advanced nephritis, 1; and increased icteric index in a patient with previous hepatitis due to sulfanilamide, 1.

The following table gives pertinent data on all cases which reverted from a positive to a negative bacterioscopy under the influence of promin therapy.

TABLE 3

Registration number	Months of treatment before first negative report	Amount of promin required before first negative report, in grams	Number of negatives	Registration number	Months of treatment before first negative report	Amount of promin required before first negative report, in grams	Number of negatives
869	24	1,926	1	1417	8	365	1
1229	13	298	1	1500	8	427	1
1413	24	[1]519	2	817	7	794	1
575	9	948	3	1123	6	692	3
1196	11	756	1	1492	6	240	3
1343	10	485	1	1514	6	373	1

[1] In addition to 233 gm. of sulfathiazole.

Because leprosy is a chronic disease subject to periods of spontaneous remissions more or less prolonged, it may be difficult to determine whether improvement under any new experimental treatment is entirely due to the remedy under study or not. However, the writers feel that the large number of patients showing improvement in contrast to the small number in whom unfavorable progress was made under promin therapy cannot well be explained on the basis of spontaneous improvement alone.

To test this impression a control experiment was undertaken with a prominlike drug, Internal Antiseptic 307, which was administered orally in capsules to one group of patients while a placebo, lactose with a trace of quinine, in similar capsules was given to another group of patients. The placebo was similar in appearance and taste to the active drug, and none of the patients taking it suspected that they were not being actively treated. Internal Antiseptic 307 chemically is sodium-4,4′-diaminodiphenylsulfone-2-acetylsulfonamide. Being closely related chemically to promin, it was found to have a similar action in leprosy. It was chosen for oral administration

instead of promin, which is too toxic when given by mouth. Internal Antiseptic 307 is a Parke Davis product and was furnished gratis by this firm for this experiment.

There was less objection in this institution to the administration of a placebo orally than by the intravenous route, as it would have been more difficult to manage a control series of patients on intravenous injections without arousing their suspicion. The group of patients taking the I. A. 307 and those of the control group were closely matched as to type and stage of the disease. The dosage of the drug and of the placebo were the same, varying from 5 to 15 gr. daily and averaging 10 gr. It was necessary to use these small doses of I. A. 307 to obviate toxic reactions, since this drug has cumulative properties. The patients of both groups were handled in exactly the same manner. During the course of treatment complete blood counts and urinalyses were done every 2 weeks on all patients of both groups. Antianemic therapy was administered to patients of either group whenever indicated by the laboratory findings.

After a period of over 8 months it became apparent that there was a difference in the condition of the two groups of patients. While the course of the disease continued unabated in the control group, it was checked in a considerable percentage of the treated patients. Complications of the disease, such as ulcerations, rhinitis, laryngitis, and iridocyclitis, frequently improved under I. A. 307 but were unaffected in the control patients. A comparison of the results after more than 9 months of treatment is given for the two groups in Table 4. In this table under complications are included: chronic ulcerations, leprous rhinitis, leprous laryngitis, and iridocyclitis.

Data in the above table seem to indicate that improvements in leprosy under promin and prominlike drugs cannot be attributed only to spontaneous remissions in the course of the disease.

CONCLUSIONS

Promin is the sulfonamide drug which thus far seems to possess to the greatest extent some chemotherapeutic properties against leprosy.

While no direct evidence of a specific bacteriostatic or bacteriocidal action against *M. leprae* has been demonstrated, it has been observed that promin appears capable of inhibiting the progress of leprosy in a considerable percentage of cases. As yet no case of leprosy has become arrested under its influence.

It is found that promin can be safely administered intravenously for prolonged periods, provided the blood and urine are examined frequently. When these precautions are taken, toxic manifestations are relatively rare and mild. The most important of them, hemolysis, if recognized early, is usually controllable and not a cause for discontinuance of treatment.

Further experimental and clinical studies on the treatment of leprosy with promin must be conducted before more definite conclusions can be drawn as to its therapeutic value.

It is not claimed that promin is a specific for leprosy, but in the writers' estimation it is an advance in the right direction in the therapy of this disease.

Promin can be considered to have opened a new avenue in the chemotherapy of the mycobacterial diseases. It is hoped that further synthesis of sulfa compounds may

TABLE 4

	Internal Antiseptic 307	Control
Number of patients	20	20
Improvement in leprosy	6 (30 percent)	1 (5 percent)
No change in leprosy	5 (25 percent)	9 (45 percent)
Leprosy worse	3 (15 percent)	5 (25 percent)
Improvement limited to complications	5 (25 percent)	0.
Complications worse	1 (10 percent)	5 (25 percent)
Bacterioscopy becoming negative	2	0.

produce a substance which will succeed in saving countless lives in this still dark field of medicine.

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