THE PRESENT STATUS OF THE SULFONES IN THERAPY[1]

E. A. SHARP, M. D.
Director, Department of Clinical Investigation
and E. H. PAYNE, M. D.
Of the Department of Clinical Investigation
Parke, Davis and Company, Detroit, Michigan

PROMIN

Synthesis of diaminodiphenyl sulfone was reported in 1908 by Fromn and Whittmann (1) during their researches in dye chemistry. Not until 1937 did Buttle (2) and his associates initiate interest in the compound by their chemotherapeutic studies against streptococcic infections in mice. They found the compound 100 per cent more effective than sulfanilamide. On August 5 of the same year, Tuller made diaminodiphenyl sulfone in the research laboratories of Parke, Davis and Company, and the following day Tillitson made the compound soluble by converting it into promin. From that date to the present, chemical and laboratory work on sulfone compounds have continued without interruption.

Beginning in late 1937, laboratory and clinical studies of promin spread over the general field of infectious diseases. It proved to be of value in certain conditions such as streptococcic infections and certain types of pneumonia, and it also gave encouraging results in those conditions where it is necessary to give a chemotherapeutic agent intravenously.

A complete change occurred in the attitude and interest of the medical profession toward the sulfones following the work of Feldman and Hinshaw (20). They began working on experimental tuberculosis in guinea pigs in 1940, the same year that Rist, Block, and Harmon (13) reported the inhibitory effect of diaminodiphenyl sulfone upon tuberculosis in animals. Also this same year Bambas (55) made promizole.

The studies of Feldman and Hinshaw were enlarged and extended in this study of sulfone compounds, until an extensive number have been evaluated, and new compounds, as they are made, are placed on experimental trial.

---

[1] Read at the Fifth International Leprosy Congress, Havana, on April 5, 1948. This paper is regarded as of special interest because of the bibliography of the sulfones.—EDITOR.

Promising results of promin in the treatment of animal tuberculosis stimulated Cowdry (17) to try the same drug for the treatment of rat leprosy. His results, published in October 1941, were encouraging but not as spectacular as those in the tuberculosis experiments. One observation in Cowdry's paper is significant. It is that the degree of granulation of the bacilli in the periphery of the nodules (i. e., in those nearest the circulating blood), appeared to be greater in the treated animals than in the untreated. This same change was first noticed by Eccles while making a microscopic study of biopsy specimens from treated leprosy patients at the U. S. National Leprosarium at Carville, Louisiana. Promin was first made available to Faget at Carville in January, 1941. In selecting cases for his study he chose lepromatous patients who were in an advanced stage of the disease. This fact made the beneficial results all the more spectacular to the observer, but was difficult to convey in the literature.

The first investigator among Faget's group to become convinced of the effectiveness of promin was Prejean (154), the dentist. Since oral and pharyngeal lesions are among the earliest to respond to sulfone treatment, Prejean had an opportunity to observe the first beneficial effects of the new drug.

Late in 1942, the first study of promin in treatment of Hansen's disease outside the United States was begun in the city of Trinidad, Bolivia. This study was conducted by Dr. Juan Jablomsky who, due to the exposures resulting from his work, contracted pernicious malaria which resulted in his sudden death.

Faget (59) published his first report on the treatment of Hansen's disease with promin on November 26, 1943, three years after publication of the first tuberculosis study by Feldman and associates.

TOXICITY OF PROMIN

Due to the interest following Feldman and Hinshaw's announcement of the results of promin treatment in guinea pig tuberculosis, the manufacturer was deluged with requests for supplies of the compound. In order to discourage indiscriminate use, and to emphasize the need for care and control, the laboratory over-emphasized its toxic effects. It is now time that we re-evaluate our data on promin and determine its dangers in the light of present knowledge and experience.

Beginning in 1938, this drug has been used for treatment of

various human diseases. During this ten years of clinical study, thousands of patients have received it without a single death resulting from the effects of the drug. This record cannot be equalled by sulfanilamide or sulfadiazine, which are generally considered safe. The signs of promin toxicity are not hidden as is the case with those drugs; they are easily recognized, even by nonmedical individuals, in sufficient time for reduction of the dose or discontinuance of treatment long before grave symptoms develop. Recovery is thereafter always rapid.

PROMIZOLE

Promizole, first described by Bambas, is an isoster of 4,4′-diaminodiphenyl sulfone and has a 2-aminothiazolyl radical replacing one of the aminophenyl groups. Promizole is soluble in water to the extent of 0.03 per cent, but is highly soluble in dilute acids and some organic solvents. It is stable in dry form.

Dogs on a diet containing fresh horse meat received promizole in the amount of 0.1 gm. per kilogram of bodyweight for 40 days, and developed no symptoms of toxicity except occasional periods of slight incoordination and a moderate lowering of the red cell blood count. Autopsies revealed no gross or histologic pathology. After a period of 106 days' treatment there was a suggestion of hyperplastic change in the thyroid gland. Promizole concentration in the blood reaches a maximum in four to seven hours. It is slowly excreted. In the body the compound undergoes conjugation into more soluble products. Promizole enters the spinal fluid in demonstrable amounts.

In addition to the therapeutic effectiveness of promizole in treatment of Hansen's disease, it has been used successfully in the treatment of scleroderma by Wuerthele and of miliary tuberculosis and tuberculous meningitis by Lincoln and associates.

Present difficulty of manufacture increases the cost of promizole to a point which limits its use in therapy.

PROMACETIN

This compound is sodium-4,4′diaminodiphenyl sulfone-2-acetylsulfonamide. It is a white crystalline compound which forms a 3 per cent solution in water at room temperature. Promacetin does not break down into diaminodiphenyl sulfone, which perhaps explains its low toxicity. Dogs fed one gram per kilogram of bodyweight daily for seven days showed no complications.

In man the dose has varied from 4 to 13 grams per day over periods of one week without evidence of toxicity. Physiologic

studies indicate that, even with massive doses by mouth, the blood level will seldom attain dangerous proportions. Blood levels from a single dose, however, are maintained for at least two days. This sustained blood level is not well understood physiologically, but would be a great advantage should the drug be used for mass treatment in large institutions.

Promacetin was found to be of value in certain cases of pneumonia, and presumptive trial at Carville by Faget and Johansen indicated that it may be of value in Hansen's disease.

DISODIUM FORMALDEHYDE SULFOXYLATE DIAMINODIPHENYL SULFONE[2]

This compound was synthesized simultaneously and independently by Raiziss, Clemence, and Freifelder (79,110) and by Bauer and Rosenthal (4). Muir (109) initiated the clinical study of this compound, and found it effective in controlling development and causing a remission of symptoms and signs of Hansen's disease. Faget, Pogge, and Johansen (126) and Fernandez and Carboni (146) also reported favorable results from their studies.

Intolerance to this compound has been reported in a wider variety of reactions than in the case of promin.

DICINNAMYL SODIUM SULFONATE DIAMINO DIPHENYL SULFONE[3]

This compound is bis (3″-phenylpropyl-1″,3″-disodium sulfonate) -4,4′-diaminodiphenyl sulfone. It has a molecular weight of 892 and contains 27.8 per cent of 4,4′-diaminodiphenyl sulfone. It is very soluble in water, and readily decomposes in an acid medium to give 4,4′-diaminodiphhenyl sulfone.

Wharton (156) and Dharmendra and Chatterjee (159) have used this drug in treatment of Hansen's disease and report satisfactory results from their preliminary studies.

BENADRYL

Benadryl gives promise of being of great value as an adjunct in treatment of Hansen's disease. Mom (153) and Wharton (158) report it to be highly effective in controlling lepra reactions. This will remove one of the annoying complications of sulfone therapy, as well as furnish relief from one of the most distressing syndromes of untreated Hansen's disease.

---

[2] Diasone (Abbott Laboratories), diamidin (Parke, Davis and Company).—EDITOR.

[3] Sulfetrone.—EDITOR.

PRESENT RESEARCH

Research in the field of the mycobacteria is divided into two stages. The first stage is being carried on in several laboratories which are actively screening numerous compounds both *in vitro* and *in vivo*. Therapeutic studies against animal tuberculosis are extensive. Those studying treatment of rat leprosy are more limited in numbers.

After a compound proves to be effective in the laboratory it is prepared for the second or clinical stage. This preparatory stage comprises exhaustive studies of tolerance and toxicity. Standards of purity must be determined, and methods of testing for blood and urine concentrations established. Testing tolerance and toxicity includes both animal studies and studies on human volunteers.

When the pharmacology and toxicology of a new compound are well understood it is ready for the clinician. Clinical evaluation of chemotherapeutic substances for Hansen's disease is a long and painstaking process. In the search for new drugs the factors involved are increased rapidity of action and greater tolerance. The Leonard Wood Memorial is the logical entity to facilitate these clinical studies and to aid in the interchange of information.

NEW COMPOUNDS

Certain sulfone compounds found to be effective in the laboratory have not as yet had clinical trials. These compounds have some chemical and physical characteristics which are of advantage.

MONOPROPYL DIAMINODIPHENYL SULFONE

The chemical name of this compound is 4-propylamino-4′ aminodiphenyl sulfone. It is a white crystalline solid which is only slightly soluble in dilute mineral acids and organic solvents. It has a molecular weight of 290 and contains the equivalent of 85.6 per cent of 4,4′-diaminodiphenyl sulfone. The side-chain cannot be readily split from the amino group.

MONOALLYL DIAMINODIPHENYL SULFONE

The chemical name of this compound is 4-allylamino-4′ amino diphenyl sulfone. It is a yellowish white crystalline product which turns yellow on prolonged exposure to light. It is slightly soluble in organic solvents. It differs from the above compound by having a double bond in the side chain. It has a molecular weight of 288 and contains the equivalent of 86.0 per cent of

4,4′-diamino diphenyl sulfone. The allyl group can not be readily split from the amino group.

ACETYL PROMIZOLE

This compound is a derivative of promizole, in which the acetyl group is attached to the amino group on the thiazole nucleus. Since promizole contains no 4,4′-diaminodiphenyl sulfone, this compound also contains none. It is quite insoluble in water and dilute mineral acids, soluble in dilute alkaline solutions. Its molecular weight is 297.

Clinical evaluation of these compounds cannot be determined until a carefully controlled comparative study is arranged with compounds of known efficacy. The time is rapidly approaching when such a study will be indicated.

CONTROL OF SULFONE DRUGS

A suggestion has been made that the sulfone drugs be placed under some type of international control, in such a way that their use can be directed and their distribution limited for reasons of efficiency. We have seen that the use of the sulfones is not limited to the treatment of Hansen's disease. Their usefulness in general chemotherapy is recognized by many physicians. They are being used in treating various forms of tuberculosis, streptococcic infections, scleroderma and other conditions of less importance. Therefore this Congress would be encroaching on the field of general therapy should it advise any method of control.

Any political or economic crisis increases the ease with which bureaucratic power usurps the freedom of the individual. These are times when the medical profession must be on the alert to guard its ancient art and traditional freedom. Bureaucracy is a dark cloud attempting, in many lands, to smother the inherent liberties of the free practice of medicine, trying to reduce this ancient and respected art to the level of political decree. Let us be jealous of the liberties we still retain, and not encourage further smothering of our profession by governmental agencies.

I believe this Congress will agree that any governmental control of these drugs will increase the hardships of the individual physician in the pursuit of his profession. It will also directly or indirectly increase the cost of medication to the patient, or to the institution which has assumed his treatment and care.

Controlling the use of a drug by govermental decree requires

the organization of a bureau consisting of numerous salaried personnel for the purpose of enforcing the control regulations. The salaries and other expenses of such a bureau are added directly or indirectly to the cost of the product. Often the personnel in such a bureau are not medical men, and as a result they lack sympathy or understanding of the medical problems involved. Such a program is the practice of medicine by decree, and if carried to its logical conclusion it would, in the end, result in slot-machine prescribing with no doctor being necessary.

When the Federal Government assumes the role of sole distributor of a drug the evils are still further multiplied. Not only is there great expense in such a program, but also the profession of medicine is subjected to the unnecessary delay and annoyance of the unavoidable red tape involved. Such a plan would limit use of the drugs to the extent that doctors living in the interior would not find them easily available, and the profession in general would be dependent upon political patronage for what is considered a traditional right and privilege.

Would it not be easier, for all concerned, to limit the sale of these compounds by duly licensed pharmacies to or on the prescription of licensed physicians? Such a regulation would neither interfere with shipments or supplies of the drugs as would most other forms of regulation, nor would it add to the cost or inconvenience the patient or physician. This is the only control which would not interfere with the ethical practice of medicine, and at the same time it is the only control which would insure the prompt and adequate care and treatment of the sick in all communities. Such supervision would also afford the maximum amount of protection against the abuse and dangers of nonprofessional medication.

Let us be jealous of surrendering our professional liberty, because liberty and freedom once lost are difficult to regain.

BIBLIOGRAPHY

(1908)

1. FROMM, E. and WITTMANN, J. Derivate des p-nitrothiophenols. Ber. d. deutsch. chem. Gesellsch. **41** (1908) 2264.

(1937)

2. BUTTLE, G. A. H., STEPHENSON, D., SMITH, S., DEWING, T. and FOSTER, G. E. Treatment of streptococcal infections in mice with 4:4′ diamino-diphenyl-sulphone. Lancet **1** (1937) 1331.
3. FOURNEAU, E., NITTI, F., TREFOUEL, J., BOVET, D. and TREFOUEL, J. (MME.) Action antistreptococcique des derives sulfures organiques. Compt. rend. Acad. d. sc. **204** (1937) 1763.

(1938)

4. BAUER, H. and ROSENTHAL, S. M. Studies in chemotherapy; some new sulphur compounds active against bacterial infections. Pub. Health Rep. **53** (1938) 40.

(1939)

5. GREEY, P. H., MACLAREN, D. B. and LUCAS, C. C. Chemotherapy in experimental pneumococcal infections. Canadian Med. Assn. J. **40** (1939) 319.

(1940)

6. CHRISTIE, W. L. Actinomycosis. Bull. Toronto East Med. Assn. **5** (1940) 6.
7. FELDMAN, W. H., HINSHAW, H. C. and MOSES, H. E. Effect of promin on experimental tuberculosis; preliminary report. Proc. Staff Meet., Mayo Clin. **15** (1940) 695.
8. JOHNSON, R. M. Absence of toxic manifestations following parenteral administration of promin. Proc. Central Soc. Clin. Res., J. American Med. Assn. **114** (1940) 520.
9. KEMPER, W., WISE, B. and SCHLAYER, C. Manometric determinations of the effects of various sulfanilamide compounds on brucella melitensis. American J. Med. Sci. **200** (1940) 484.
10. MITCHELL, D. R., GREIG, C. H. and UREN, J. L. Treatment of gonorrhoea by chemotherapy (preliminary note). Canadian Med. Assn. **42** (1940) 533.
11. TOOMEY, JOHN A., CASPARIS, H., HUENEKENS, E. J., MCKHANN, C. F., SCHICK, B. and SHAW, E. B. Report of the committee on immunization and therapeutic procedures for infectious diseases of the American Academy of Pediatrics. (Revised October, 1940.)
12. WILE, U. J. and HOLMAN, H. H. Acute disseminated lupus erythematosus; its treatment with sulfanilamide and allied products. Arch. Dermat. & Syph. **42** (1940) 1059.
13. RIST, N., BLOCK, F. and HAMON, V. Action inhibitrice du sulfonamide et sulfonamide et d'une sulfone sur la multiplication in vivo et in vitro du bacille tuberculeux aviaire. Ann. Inst. Pasteur **64** (1940) 203.

(1941)

14. ARDLEY, D. G. The common sulfonamides. Lancet **2** (1941) 625.
15. BUSTAMENT, E. Promin (diaminosulfone derivative); review of literature. Rev. Chilena Pediat. **12** (1941) 874.
16. COGGESHALL, L. T., MAIER, J. and BEST, C. A. Effectiveness of two new types of chemotherapeutic agents in malaria; sodium p,p′-diamino-diphenyl-sulfone N,N′-didextrose-sulfonate (promin) and 2-sulfanilamide pyrimidine (sulfadiazine). J. American Med. Assn. **117** (1941) 1077.
17. COWDRY, E. V. and RUANGSIRI, C. Influence of promin, starch and ~~hepatalhyde~~ aldehyde on experimental leprosy in rats. Arch. Path. **32** (1941) 632.
18. EDITORIAL. Chemotherapy for tuberculosis. British Med. J. **2** (1941) 856.
19. EDITORIAL. New sulfonamide compounds. British Med. J. **1** (1941) 861.

20. FELDMAN, W. H., HINSHAW, H. C. and MOSES, H. E. The treatment of experimental tuberculosis with promin (sodium salt of p,p′-diamino-diphenyl-sulfone-N,N′ dextrose sulfonate): a preliminary report. Proc. Staff Meet., Mayo Clin. **16** (1941) 187.
21. FELDMAN, W. H., HINSHAW, H. C. and MOSES, H. E. The treatment of experimental tuberculosis with promin (sodium salt of p,p′-diamino-diphenyl-sulfone-N,N′ dextrose sulfonate). American J. Path. **17** (1941) 578.
22. HINSHAW, H. C. and FELDMAN, W. H. Treatment of experimental tuberculosis; use of sodium p,p′-diamino-diphenyl-sulfone-N,N′-didextrose sulfonate ("promin"); with notes on toxic effects observed in man. J. American Med. Assn. **117** (1941) 1066.
23. KENDELL, H. W., ROSE, D. L. and SIMPSON, W. M. Combined artificial fever-chemotherapy in gonococcic infections resistant to chemotherapy. J. American Med. Assn. **116** (1941) 357; (Abstr.) Artificial fever versus combined fever-chemotherapy in gonococcic infections. Arch. Phys. Therapy **22** (1941) 103.
24. MITCHELL, D. R. and COTE, F. H. Sodium sulfathiazole in urology. Canadian Med. Assn. J. **44** (1941) 240.
25. ROSE, D. L., KENDELL, H. W. and SIMPSON, W. M. Refractory gonococcic infections; elimination by combined artificial fever and chemotherapy as related to military medicine. War Med. **1** (1941) 470.
26. SCHMIDT, E. R., CURRERI, A. R., HIDDE, F. G. and ADASHEK, E. P. Peritoneal vaccination, irrigation and chemotherapy in treatment of experimental peritonitis. Surgery **9** (1941) 470.
27. TAYLOR, A. D. Present status of fever therapy. Southern Med. & Surg. **103** (1941) 595.
28. TOOMEY, J. A. and DICE, M. E. Blood promin levels in man. J. Pediat. **18** (1941) 6.
29. TOOMEY, J. A. and ROACH, F. E. Promin in the treatment of some acute infections. J. Pediat. **18** (1941) 1.
30. TOOMEY, J. A. and TAKACS, W. S. Attempts to produce urinary concretions in monkey with promin. J. Pediat. **18** (1941) 10.

(1942)

31. BARACH, A. L., MOLOMUT, N. and SOROKA, M. Inhalation of nebulized promin in experimental tuberculosis; sodium p,p′-diamino-diphenyl-sulfone-N,N′-didextrose sulfonate. American Rev. Tuberc. **46** (1942) 268.
32. EDITORIAL. Chemotherapy and tuberculosis. Minnesota Med. **25** (1942) 375.
33. EMMART, E. W. and SMITH, M. I. The attenuating effect of promin on virulence of the tubercle bacillus. Proc. Soc. Exper. Biol. & Med. **51** (1942) 320.
34. FELDMAN, W. H. Chemotherapy in experimental tuberculosis (John W. Bell Tuberculosis Lecture). Minnesota Med. **25** (1942) 339.
35. FELDMAN, W. H., HINSHAW, H. C., MANN, F. C. and MOSES, H. E. Effect of promin on experimental tuberculosis in guinea pig. Nat. Tuberc. Assn. Trans. **38** (1942) 74.
36. FELDMAN, W. H., MANN, F. C. and HINSHAW, H. C. Promin in experimental tuberculosis; observations on tuberculous guinea pigs

before and after treatment with sodium p,p′-diamino-diphenyl-sulfone-N,N′-didextrose sulfonate (promin). American Rev. Tuberc. **46** (1942) 187.

37. FELDMAN, W. H., HINSHAW, H. C. and MOSES, H. E. Promin in experimental tuberculosis; sodium p,p′-diamino-diphenyl-sulfone-N,N′-didextrose sulfonate. American Rev. Tuberc. **45** (1942) 303.
38. FOSTER, R. C. Gonococcus bacteremia with joint skin manifestations; a case report. Ann. Int. Med. **16** (1942) 1018.
39. HALL, B. E., PFUETZE, K., HINSHAW, H. C. and FELDMAN, W. H. Effect of promin on the blood of patients with tuberculosis; preliminary report. Proc. Staff Meet., Mayo Clin. **17** (1942) 24.
40. HALL, B. E., HINSHAW, H. C. and PFUETZE, K. Observation on the effect of promin on the blood of tuberculous patients. J. Clin. Invest. (Proc.). **21** (1942) 632.
41. HELMHOLZ, H. F. Chemotherapy with the sulfonamide compounds. Wisconsin Med. J. **41** (1942) 472.
42. HIGGINS, G. M. Certain toxic effects upon the hematopoietic system of guinea pigs induced by promin (sodium p,p′-diamino-diphenyl-sulfone-N,N′-didextrose sulfonate). Anat. Rec. (Proc.). **82** (1942) 421.
43. HINSHAW, H. C., PFUETZE, K. and FELDMAN, W. H. Progress report; observations on the use of promin in clinical tuberculosis. (Abstract of paper presented before the National Tuberculosis Association in Philadelphia, May 8, 1942.)
44. MELLON, R. R. Tuberculosis chemotherapy (promin, diamino-sulfone derivative). Dis. of Chest **8** (1942) 166.
45. REED, G. B. and ORR, J. H. Local chemotherapy of experimental gas gangrene. War Med. **2** (1942) 59.
46. SCHLOTTHAUER, C. F. Treatment of equine encephalomyelitis (Western) with certain sulfonamide compounds; experimental study. Proc. Staff Meet., Mayo Clin. **17** (1942) 187.
47. SCIENCE NEWS LETTER. Sulfone drug effective weapon against tuberculosis. Sci. News Letter **41** (1942) 131.
48. SCIENCE NEWS LETTER. Human trials of chemical for tuberculosis succeed. Sci. News Letter **41** (1942) 307.
49. SCIENCE, SUPPLEMENT. A new chemical remedy for tuberculosis. Science, Suppl. **95** (1942) 8.
50. SMITH, M. I., EMMART, E. W. and WESTFALL, B. B. The action of certain sulfonamides, sulfones and related phosphorus compounds in experimental tuberculosis. J. Pharmacol. & Exper. Therap. **74** (1942) 163.
51. THE STAR. Promin in Hansen's disease. The Star, U. S. Marine Hospital, Carville, La., (1942) 5 (Oct.).
52. STEINBACH, M. M. and DUCA, C. J. Promin in treatment of experimental tuberculosis. Proc. Soc. Exper. Biol. & Med. **49** (1942) 460.
53. TYTLER, W. H. and LAPP, A. D. Treatment of superficial tuberculous lesions by local application of promin. British Med. J. **2** (1942) 748.
54. ZUCKER, G., PINNER, M. and HYMAN, H. T. Chemotherapy of tuberculosis; promin by the intravenous drip method. American Rev. Tuber. **46** (1942) 277.

55. BAMBAS, L. L. Abstracts of papers presented at the 103rd meeting of the American Chemical Society, Memphis, Tennessee, April 20-24, 1942.

(1943)

56. CALLOMON, F. F. T. New derivatives of diamino-diphenyl-sulfone; their therapeutic effect in experimental tuberculosis of guinea pigs. American Rev. Tuberc. **47** (1943) 97.

57. CRAWFORD, J. H. Promin in tuberculosis. Lancet **1** (1943) 787.

58. EDITORIAL. Chemotherapeutic agents and experimental tuberculosis. J. American Med. Assn. **121** (1943) 763.

59. FAGET, G. H., POGGE, R. C., JOHANSEN, F. A., DINAN, J. F., PREJEAN, B. M. and ECCLES, C. G. The promin treatment of leprosy; a progress report. Pub. Health Rep. **58** (1943) 1729.

60. FELDMAN, W. H. and HINSHAW, H. C. Comparative effects of six compounds administered with therapeutic intent to guinea pigs. American J. Clin. Path. **13** (1943) 144.

61. FELDMAN, W. H. and HINSHAW, H. C. Promin in experimental tuberculosis; comparative results of continuous and of intermittent treatment of tuberculous guinea pigs with sodium p,p′-diamino-diphenyl-sulfone-N,N′-didextrose sulfonate (promin). American Rev. Tuberc. **48** (1943) 256.

62. FELDMAN, W. H. and HINSHAW, H. C. Tuberculochemotherapy. Journal-Lancet **63** (1943) 116.

63. FREIJO, J. C. Los derivados sulfamidicos y similares en tratamiento de la tuberculosis; revista de las literatura aparecideo a los ultimo anus, con especial referencia a los ensayos efectuados con la promin. Hoja Tisiol. **3** (1943) 123.

64. HAYES, D. S. Local application of promin in tuberculous lesions. British Med. J. **1** (1943) 81 (Corresp.)

65. HEAF, F. R. G., HURFORD, J. V., EISER, A. and FRANKLIN, L. M. Tuberculosis treated with promin. Lancet **1** (1943) 702.

66. HIGGINS, G. M. The effect on erythrocytes of a single administration of promin (sodium p,p′-diamino-diphenyl-sulfone-N,N′-didextrose sulfonate); an experimental study. American J. Clin. Path. **13** (1943) 28.

67. HIGGINS, G. M. Toxic effects of promin (sodium p,p′-diamino-diphenyl-sulfone-N,N′-didextrose sulfonate) on the erythrocytes of guinea pigs. American J. Med. Sc. **205** (1943) 834.

68. HIGGINS, G. M. The use of promin (sodium p,p′-diamino-diphenyl-sulfone-N,N′-didextrose sulfonate) in nutrition experiments. Anat. Rec. **85** (1943) 318.

69. HINSHAW, H. C., PFUETZE, K. and FELDMAN, W. H. Treatment of tuberculosis with promin; a progress report. American Rev. Tuberc. **47** (1943) 26.

70. KIRK, H. Promanide (promin) in the treatment of tuberculosis. Vet. J. **99** (1943) 156.

71. LURIE, M. B. and STOKES, J., JR. The effect of promin on experimental tuberculosis in the rabbit. J. Bacteriol. **45** (1943) 194.

72. MEDLAR, E. M. and SASANO, K. T. Promin in experimental tuberculosis in the guinea pig. American Rev. Tuberc. **47** (1943) 618.

73. QUERIES & MINOR NOTES. Sulfone compounds for pulmonary tuberculosis J. American Med. Assn. **121** (1943) 798.
74. SMITH, M. I., EMMART, E. W. and STOHLMAN, E. F. The action of some derivatives of 4,4′-diamino-diphenyl-sulfone in experimental tuberculosis. American Rev. Tuberc. **48** (1943) 32.
75. STEENKEN, W., JR. and HEISE, F. H. Action of promin and diamino-diphenyl sulfone upon tubercle bacilli; antipromin action of p-aminobenzoic acid. Proc. Soc. Exper. Biol. & Med. **52** (1943) 180.
76. STEENKEN, W., JR., HEISE, F. H. and WOLINSKY, E. Treatment of experimental tuberculosis in the vaccinated and nonvaccinated guinea pig with promin. American Rev. Tuberc. **48** (1943) 453.
77. STEINBACH, M. M. and DUCA, C. J. Chemotherapy in tuberculosis. Tuberculology **6** (1943) 93.
78. FELDMAN, W. H., HINSHAW, H. C. and MOSES, H. E. Therapeutic effects of disodium formaldehyde sulfoxylate diamino-diphenyl-sulfone in experimental tuberculosis. Arch. Path. **36** (1943) 64.
79. RAIZISS, G. W. Diasone, new and active chemotherapeutic agent. Science **98** (1943) 350.

(1944)

80. ANDERSON, H. H. and SOONG, H. Y. Promin on experimental leishmaniasis (hamsters). Fed. Proc. **3** (1944) 64.
81. ARMSTRONG, A. R., RAE, M. V., LUCAS, C. C. and CREEY, P. H. Effects of promin on experimental tuberculosis. American Rev. Tuberc. **50** (1944) 160.
82. CALLOMON, F. F. T. and GROSKIN, L. Therapeutic effect of some new derivatives of di-amino-phenyl-sulfone in experimental tuberculosis of guinea pigs. Tuberculology **7** (1944) 21.
83. DANCEY, R. J., SCHMIDT, R. H., JR. and WILKIE, J. M. Promin in pulmonary tuberculosis; progress report. American Rev. Tuberc. **49** (1944) 510.
84. EDELSTON, B. G. Treatment of a tuberculous operation wound by local application of promanide jelly. Tubercle **25** (1944) 108.
85. EDITORIAL. Chemotherapy in tuberculosis. J. American Med. Assn. **125** (1944) 149.
86. EDLIN, J. S., BOBROWITZ, I. D., SAFFORD, F. K., JR. and BUTLER, F. S. Promin inhalation therapy in pulmonary tuberculosis. American Rev. Tuberc. **50** (1944) 543.
87. FELDMAN, W. H., HINSHAW, H. C. and MANN, F. C. The effects on experimental tuberculosis of 4, 2′-diamino-phenyl-5′-thiazole-sulfone (promizole); a preliminary report. Proc. Staff Meet., Mayo Clin. **19** (1944) 25.
88. FELDMAN, W. H., HINSHAW, H. C. and MANN, F. C. The effects on experimental tuberculosis of 4,4′-diphenyl-sulfone. American J. Med. Sc. **207** (1944) 290.
89. FELDMAN, W. H., HINSHAW, H. C. and MANN, F. C. Promizole in tuberculosis; the effect on previously established tuberculosis of guinea pigs of 4,2′-diamino-phenyl-5′-thiazolyl-sulfone (promizole). American Rev. Tuberc. **50** (1944) 418.
90. HIGGINS, G. M. and FELDMAN, W. H. Effect of yeast upon the toxic reactions of promin on tuberculous guinea pigs. American Rev. Tuberc. **49** (1944) 179.

91. HIGGINS, G. M. The relation of vitamin B to the toxicity of promin as tested by the self-selection method. American J. Med. Sc. **207** (1944) 289.

92. HIGGINS, G. M. and LARSON, R. A. Hyperplasia of the thyroid gland induced by 4,2′-diamino-phenyl-5′-thiazole-sulfone (promizole). Proc. Staff Meet., Mayo Clin. **19** (1944) 137.

93. HIGGINS, G. M. Relation of vitamin B to the toxicity of promin. Proc. Staff Meet., Mayo Clin. **19** (1944) 202.

94. HIGGINS, G. M. The influence of purified diets upon the toxicity of promin. American J. Clin. Path. **14** (1944) 278.

95. HINSHAW, H. C., PFEUTZE, K. H. and FELDMAN, W. H. Chemotherapy of clinical tuberculosis with promin; p,p′-diamino-diphenyl-sulfone-N,N′-didextrose sulfonate; second report of progress. American Rev. Tuberc. **50** (1944) 52.

96. HOPKINS, R. and FAGET, G. H. Recent trends of leprosy in the United States; report of 700 cases at the national leprosarium. J. American Med. Assn. **126** (1944) 937.

97. KEITH, H. M. Use of chemotherapy in a case of tuberculous meningitis. Proc. Staff Meet., Mayo Clin. **19** (1944) 361.

98. LLOYD, J. B. and MIDDLEBROOK, G. Bacteriostatic activity of some new derivatives of diamino-diphenyl-sulfone and naphthoquinones against the tubercle bacillus. American Rev. Tuberc. **49** (1944) 539.

99. MIDDLEBROOK, G. and LLOYD, J. B. Effects of pH, temperature and salicylate on bacteriostasis of tubercle bacilli by sulfonamides and diamino-diphenyl-sulfone. American Rev. Tuberc. **49** (1944) 535.

100. MORRISON, J. B. Promanide therapy for tuberculous empyema. Tubercle **25** (1944) 105.

101. MORROW, W. J., EPSTEIN, H. C. and TOOMEY, J. A. Promin in the treatment of tuberculous meningitis. J. Pediat. **24** (1944) 623.

102. MYERS, J. A. The treatment of tuberculosis. Mod. Med. **12** (1944) 57.

103. TYTLER, W. H. Sulphone compounds in the chemotherapy of tuberculosis; a review of experimental results and pharmacological data. Tubercle **25** (1944) 95.

104. WASSERSUG, J. D. Medical progress; tuberculosis. New England J. Med. **230** (1944) 45.

105. WERNER, A. E. A. The estimation of promin in blood and urine, and a study of its excretion. Irish J. Med. Sci. (1944) 189.

106. DESMEULES, R., ROUSSEAU, L., GIROUX, M. and RICHARD, P. La diasone dans la tuberculose pulmonaire. Laval Med. **9** (1944) 780.

107. GIROUX, M. Traitement de la tuberculose experimentale du cobaye par la "diasone"; primo-infection; reinfection. Laval Med. **9** (1944) 788.

108. MUIR, E. Leprosy in British West Indies and British Guiana. Internat. J. Leprosy **10** (1942) 96; Caribbean Med. J. **6** (1944) 17.

109. MUIR, E. Preliminary report on diasone in the treatment of leprosy. Internat. J. Leprosy **12** (1944) 1.

110. RAIZISS, G. W., Clemence, L. W. and Freifelder, M. Synthesis and

chemical properties of diasone. J. American Pharm. Assoc. (Scient. Ed.) **33** (1944) 43.

(1945)

111. CURRENT COMMENT. Streptomycin and promin in experimental tuberculosis. J. American Med. Assn. **129** (1945) 620.
112. DRUG TRADE NEWS. Promin is called best drug so far used for leprosy. Drug Trade News **20** (1945) 42.
113. FAGET, G. H. and POGGE, R. C. The therapeutic effect of promin in leprosy. Pub. Health Rep. **60** (1945) 1165.
114. FELDMAN, W. H. and HINSHAW, H. C. Promin in experimental tuberculosis; effects of prolonged treatment with sodium p,p′-diamino-diphenyl-sulfone-N,N′-didextrose sulfonate (promin) on subsequent reinfection. American Rev. Tuberc. **51** (1945) 268.
115. HIGGINS, G. M. A study of the goitrogen, promizole, with reference to the thyroid, metabolism and the blood. American J. Med. Sc. **210** (1945) 347.
116. HINSHAW, H. C., FELDMAN, W. H. and PFUETZE, K. H. Present status of chemotherapy in tuberculosis. Ann. Int. Med. **22** (1945) 696.
117. HINSHAW, H. C. and FELDMAN, W. H. ..Observations on chemotherapy of clinical and experimental tuberculosis. Med. Clin. North America **29** (1945) 918.
118. MURPHY, J. A. R. "Promin" in tuberculosis; a short preliminary review accompanied by short clinical notes of the use of "promin jelly" (5%) in eleven cases. Med J. Australia **2** (1945) 310.
119. ROBIN, I. G. Treatment of tuberculous laryngitis with promin (promanide). Tubercle **26** (1945) 186.
120. SMITH, M. I., MCCLOSKY, WM. T. and EMMART, E. W. Influence of streptomycin and promin on proliferation of tubercle bacilli in the tissues of albino rat. Proc. Soc. Exper. Biol. & Med. **62** (1946) 157; *abst.* Fed. Proc. **5** (1946) 204; Pub. Health Rep. **60** (1945) 1129.
121. SMITH, M. I. and MCCLOSKY, W. T. Chemotherapeutic action of streptomycin and promin in experimental tuberculosis. Pub. Health Rep. **60** (1945) 1129.
122. WANG, S. L. and GONZALEZ-IMAN, F. C. Promin in the treatment of renal tuberculosis. J. Urol. **53** (1945) 769.
123. WASSERSUG, J. D. Medical progress; tuberculosis. New England J. Med. **233** (1945) 467.
124. WILSON, J. L. The general treatment of pulmonary tuberculosis. Clinics **4** (1945) 891.
125. ALARCON, D. G. and GARCIA SALAZAR, E. Quimioterapia de la tuberculosis; resultado de ensayos con diasone. Gac. Med. Mexico **75** (1945) 316.
126. FAGET, G. H. and POGGE, R. C. Treatment of leprosy with diasone; preliminary report. New Orleans Med. & Surg. J. **98** (1945) 145.

(1946)

127. CALLOMON, F. T. and RAIZISS, G. W. Diamino-diphenyl-sulfone derivatives; the therapeutic effects of two new derivatives in experimental tuberculosis. American Rev. Tuberc. **53** (1946) 374.

128. PARDO CASTELLO, V., TIANT, F. R., MESTRE, J. J., PEREZ, R. I. and TRESPALACIOS, F. El tratamiento de la lepra por el promin. Bol. Soc. Cubana Derm. Sifil. **3** (1946) 12.

129. DAHLBOM, R. and EKSTRAND, T. Sulfides and sulfones containing an aminothiazole group. Svensk Kem. Tids. **57** (1945) 229; Chem. Abs. 40 (1946) 4061.

130. EDITORIAL. Streptomycin-promin therapy. J. American Med. Assn. **132** (1946) 516.

131. FAGET, G. H., POGGE, R. C. and JOHANSEN, F. A. Promizole treatment of leprosy; preliminary report. Pub. Health Rep. **61** (1946) 957.

132. FITE, G. L. and GEMAR, F. Regressive changes in leprosy under promin therapy. Southern Med. J. **39** (1946) 277.

133. GRENVILLE-MATHERS, R. and PICKERING, D. Experiences with promanide in tuberculosis. British J. Tuberc. **40** (1946) 68.

134. HIGGINS, G. M. and INGLE. D. J. The relation of the hypophysis to certain changes induced in the rat by the goitrogen, promizole. Endocrinology **38** (1946) 110.

135. LEHR, H. and BLOCH, H. Chemotherapy in tuberculosis. Experientia **1** (1945) 212; C. A. **40** (1946) 3830.

136. MOM, M. [Chemotherapy of leprosy with promin: Preliminary report representing two months' clinical work.] Prensa Med. Argentina **32** (1946) 2390.

137. BRAGA PACHECO, R. Tratamiento experimental pelo sal sodico de n-n sulfonato de bidextrosa do p-p diamino-difenil-sulfona. Proc. Second Pan-American Leprosy Conference, October, 1946.

138. SCHUJMAN, S. Nuestros primeros resultados obtenidos con el promin en el tratamiento de la lepra. Proc. Second Pan-American Leprosy Conference, October, 1946.

139. SHER, B. C. and KLOECK, J. M. The combined action of p,p′-diamino-diphenyl-sulfone and immunization in experimental tuberculosis. American Rev. Tuberc. **53** (1946) 250.

140. FAGET, G. H., POGGE, R. C., JOHANSEN, F. A., FITE, G. L., PREJEAN, B. M. and GEMAR, F. Present status of promin treatment in leprosy. Internat. J. Leprosy **14** (1946) 30.

141. SMITH, M. I., MCCLOSKY, W. T. and EMMART, E. W. The influence of streptomycin and promin on the proliferation of tubercle bacilli in the tissues of the albino rat. Proc. Soc. Exper. Biol. & Med. **62** (1946) 157; *abst.* Fed. Proc. **5** (1946) 204.

142. STEENKEN, W., JR., WOLINSKY, E. and HEISE, F. H. Treatment of experimental ocular tuberculosis with promin. American Rev. Tuberc. **53** (1946) 175.

143. WASSERSUG, J. D. Medical progress; pulmonary tuberculosis. New England J. Med. **235** (1946) 220.

144. YOUMANS, G. P. and DOUB, L. The relation between chemical structure of sulfones and their bacteriostatic activity. American Rev. Tuberc. **54** (1946) 287.

145. YOUMANS, G. P., FELDMAN, W. H. and DOUB, L. A comparison of the effect of p-amino-phenyl sulfone compounds *in vitro* and *in vivo* on tubercle bacilli. American Rev. Tuberc. **54** (1946) 295.

146. FERNANDEZ, J. M. M. and CARBONI, E. A. The action of diasone in the treatment of leprosy (preliminary report). Internat. J. Leprosy **14** (1946) 19; *abst.* Trop. Dis. Bull. **44** (1947) 595.
147. MUIR, E. Virulence of lepra bacilli. Leprosy Rev. **17** (1946) 5.

(1947)

148. COCCHI, C. and PASQUINUCCI, G. Primi resultati nella terapia delle meningiti tubercolari con la streptomicina associata a solfone e vitamina A. Rev. Clin. Pediat. **45** (1947) 193.
149. FAGET, G. H. Quemoterapia de la lepra. Bol. Clin. Marly **9** (1947) 245.
150. FREEDLANDER, B. L. and FRENCH, F. A. The bacteriostatic action of benzothiazole derivatives on *M. leprae*. Exper. Med. & Surg. **5** (1947) 391.
151. GRAY, H. The chemotherapy of leprosy. New Orleans Med. & Surg. J. **100** (1947) 218.
152. JOHANSEN, F. A. Current data on promin therapy. The Star **7** (1947) 1.
153. MOM, M. Benadryl in lepra reaction of lepromatous leprosy and in sulfone sensitization. Rev. Argentina Dermatosifil. **31** (1947) No. 2.
154. PREJEAN, B. M. Chemotherapeutic effect of promin and diasone on oral lesions of leprosy. Dent. Survey **23** (1947) 1411.
155. SLOAN, N. R. Promin and other sulfones in leprosy; preliminary report. Hawaii Med. J. **7** (1947) 19.
156. WHARTON, L. H. Preliminary report on a new sulfone drug, "sulphetrone". Internat. J. Leprosy **15** (1947) 231.
157. MILGRAM, LILLIAN, LEVITT, I. and UNNA, S. Promizole treatment of miliary tuberculosis; toxic effects on thyroid gland and maturation. American Rev. Tuberc. **55** (1947) No. 2 (Feb.).
158. WHARTON, L. H. Personal communication. (1947).

(1948)

159. DHARMENDRA and CHATTERJEE, K. R. Treatment of leprosy with the sulphone drugs. Antiseptic **45** (1948) 97.
160. Lincoln, Edith M., Kirmse, W., DeVito, Estelle. Tuberculous meningitis in children. J. American Med. Assn. 136 (1948) 593.
161. Lincoln, Edith M., Stone, S. and Hoffman, Olga R. The treatment of miliary tuberculosis with promizole. Bull. Johns Hopkins Hosp. 82 (1948) 56.