

ment has led to uniformly bad results. Dilation or the forced passage of a small bronchoscope should not be attempted unless there is impending suffocation.

If a small, sharply circumscribed tuberculous ulcer should be discovered, consideration might be given to its treatment by electrocauterization with the high frequency current, as similar lesions in the larynx are often treated.<sup>16</sup> Since such a strictly circumscribed lesion seldom occurs, this therapeutic consideration is based on theoretical grounds alone.<sup>16a</sup>

Roentgen therapy in divided doses was proposed by Jacox<sup>17</sup> as a possible means of treating active tuberculous mucosal lesions on the basis that early induction of fibrosis might aid in healing, similar to the reported action of irradiation in tuberculous lymphadenitis.

The x-ray beam is directed through two ports, from 10 to 12 cm. square, centered over the lesions as localized bronchoscopically. One port is on the anterior and one on the posterior surface of the chest. The ports are treated alternately at weekly intervals, and the irradiation is continued until a definite erythema develops. This usually occurs after from six to eight treatments have been given. The physical factors are as follows: filtration, 0.25 mm. of copper and 1 mm. of aluminum; voltage, 150 kilovolts (Villard circuit); tube current, 25 milliamperes; skin target distance, 50 cm.; intensity of irradiation, from 34 to 39 roentgens per minute, measured in air without backscatter; dosage per treatment field, from 200 to 300 roentgens.

Since the treatment is experimental to a large extent, a critical evaluation of results is not justified. Eight patients have had their series of treatments completed for three months or longer. In five of the eight who had chronic hyperplastic and ulcerative lesions, bronchoscopic reexamination showed that the active lesions had regressed, although two patients with preexisting fibrostenosis have had evidence of increased scar tissue obstruction. The remaining three of the eight patients were not benefited by irradiation. One of these has shown bronchoscopically a progression of the hyperplastic disease and the recent formation of ulcers. The second had acute, extremely active hyperplastic and ulcerative disease of the lower trachea and left stem bronchus. Obstruction and sudden atelectasis of the left lower lobe followed the fifth treatment, presumably from reactionary edema and congestion of the actively diseased mucosa. The third had tracheal ulceration and moderate fibrostenosis (fig. 4). There was temporary complete relief from symptoms for two months following irradiation, but the severe dyspnea, choking attacks and asthmatoïd breathing have recently returned.

#### SUMMARY

1. A positive diagnosis of tuberculous tracheobronchitis has been made in fifty-five patients, twenty-four of these having been observed for a year or longer. On the basis of the type of lesions seen, the patients have been divided into two clinical groups which are of prognostic significance: group 1, ulcerative and stenotic, seventeen patients; group 2, nonulcerative and nonstenotic, seven patients.

2. Of the seventeen group 1 patients, none have yet returned to complete health and nine (52.9 per cent) are dead. Major collapse therapy for parenchymal pul-

monary tuberculosis has had no favorable effect on the ulcerative tracheobronchial lesions of this group.

3. Nonulcerative and nonstenotic tuberculous tracheobronchitis is considered relatively less active than ulcerative disease. For this reason collapse therapy has been recommended as indicated for the parenchymal tuberculosis. Four of the seven patients have had thoracoplasty and now have closed cavities and negative sputum. The other three have intermittently positive sputum and the relationship of this to tracheobronchial disease is not clear. Temporary paralysis of the hemidiaphragm was used in two and pneumothorax in one.

4. In selected cases symptomatic improvement has followed the bronchoscopic aspiration of retained secretions, chemical shrinkage of the edematous mucosa or the careful dilation of circumscribed bronchial stenoses.

5. Of twelve patients who have had a series of roentgen treatments, eight have been followed for three months or longer. The majority of those whose lesions were chronic, hyperplastic and granulo-ulcerative showed a regression of the disease when reexamined bronchoscopically.

6. Because of the poor results obtained in the past, we are not now recommending any type of major collapse therapy for parenchymal tuberculosis in the presence of ulcerative tuberculous tracheobronchitis unless, after bronchoscopic reexamination, it is apparent that the ulcerative lesions are healing without the formation of highly obstructive fibrosis.

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## THE USE OF SULFANILAMIDE IN GONOCOCCIC INFECTIONS

### PRELIMINARY REPORT

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During the past two years, numerous reports have appeared in the European literature regarding the action of para-aminobenzenesulfonamide (sulfanilamide) and its related compounds marketed under the proprietary names of Prontosil,<sup>1</sup> Prontylin and many other names, on both experimental and clinical infections with beta-hemolytic streptococci. Mice are protected or their survival periods significantly lengthened against many lethal doses of this organism by the administration of these drugs. The results of their use in clinical infections have been most striking. Colebrook<sup>1a</sup> has reported a series of thirty-six cases of puerperal infection with hemolytic streptococci, treated with prontosil. From this he concluded that the drug caused a definitely beneficial effect, as evidenced by a prompt improvement in symptoms, a drop in temperature and a reduction in the death rate from between 18 and 28.8 per cent to 8 per cent in his series.

The first American report was recently made by Long and Bliss,<sup>2</sup> in which their carefully controlled experimental and clinical studies corroborate and amplify many of the previous experiences. They point

From the Brady Urological Institute and the Johns Hopkins Hospital. Dr. Perrin H. Long assisted with advice and criticism in carrying out this investigation.

Owing to lack of space, reports of illustrative cases have been omitted. The complete article appears in the authors' reprints.

1. The name Prontosil has been used for several related substances that are not identical.

1a. Colebrook, Leonard, and Kenny, Méave: *Lancet* **1**: 1297 (June 6) 1936.

2. Long, P. H., and Bliss, Eleanor, A.: *Para-Amino-Benzene-Sulfonamide and Its Derivatives*, J. A. M. A. **108**: 32 (Jan. 2) 1937.

16. Terry, G. H. B.: *Electrosurgery in Laryngeal and Pharyngeal Tuberculosis*, *South. M. J.* **28**: 509-511 (June) 1935.

16a. Since the preparation of this report the lesions of several patients have been successfully treated by electrocauterization. The method apparently warrants much consideration.

17. Dr. Harold Jacox was formerly assistant professor of roentgenology in charge of therapy at the University of Michigan Medical School and at present is director of the radiation therapy division at the Western Pennsylvania Hospital, Pittsburgh.

Initial Number	Onset of Infection, Date	Treatment Previous to Sulfanilamide	Date Sulfanilamide Started	Diagnosis at Institution of Treatment	Symptomatic Improvement	Negative Smear in Days	Complications and Reaction	Days Followed	Condition on Last Visit	Comment
R. S. 1	2/15/37	None	2/18/37	Acute anterior urethritis; acute inguinal adenitis	Urethral discharge stopped 3/10/37	23	0	44	Glasses 1, 2, 3 clear, no shreds; asymptomatic	15 days' lapse from treatment and observation; last sulfanilamide on 3/13/37; Stricture dilated 3/23/37
A. E. 2	1/19/37	Urethral irrigations; alkalis internally	2/20/37	Chronic anterior and posterior urethritis; urethral stricture	Urethral discharge stopped in 3 days	3	0	28	Glasses 1, 2, 3 clear; glass 2 shows no W. B. C.; nocturia 2-3 times	
B. S. 3	1/28/37	Urethral irrigations	2/24/37	Subacute anterior and posterior urethritis	Urethral discharge, burning and nocturia stopped in 3 days	6	Lassitude and dizziness	39	Glasses 1, 2, 3 clear, no shreds; prostatic secretion normal, asymptomatic	Last sulfanilamide on 3/9/37
R. M. 4	2/22/37	Turpentine internally	2/26/37	Acute anterior urethritis	Urethral discharge and nocturia stopped in 2 days	3	0	38	Glasses 1, 2, 3 clear; glass 1 shows rare W. B. C.; prostatic secretion normal; asymptomatic	Last sulfanilamide on 3/6/37
O. L. 5	2/22/37	None	3/13/37	Subacute anterior and posterior urethritis; subacute prostatitis and seminal vesiculitis; terminal hematuria	Urethral discharge and burning stopped in 2 days	3	0	16	Glasses 1, 2, 3 clear, no shreds; glass 1 shows 1-2 W. B. C. / H. P. F.; prostatic secretion shows few clumps of W. B. C.; asymptomatic	Last sulfanilamide on 3/27/37
A. F. 6	3/14/37	None	3/20/37	Acute anterior and posterior urethritis; chronic recurrent prostatitis (16 months' duration)	Urethral discharge and burning stopped in 2 days	3	0	18	Glasses 1, 2, 3 clear, no shreds; glass 1 shows 1-2 W. B. C. / H. P. F.; prostatic secretion normal (4 times); nocturia 1 time; otherwise asymptomatic	Last sulfanilamide on 4/5/37
J. H. 7	3/18/37	None	3/24/37	Acute anterior urethritis; chronic epididymitis	Only "morning drop" after 3/29/37; this stopped 4/8/37	9 recurred in 14; again negative in 17	Recurrence; reaction	17	Glass 1 clear, with shreds; glasses 2, 3 clear; smear from fossa navicularis shows a few W. B. C.; no gonococci	Took only 0.3 Gm. of sulfanilamide 4 times a day for first 5 days of treatment
C. L. 8	1/14/37	Urethral irrigations; alkalis internally; urethral instrumentation	3/25/37	Subacute anterior and posterior urethritis	Urethral discharge and burning stopped in 2 days	5	0	12	Glasses 1, 2, 3 clear; glass 1 shows rare shred; glass 2 shows 1-2 W. B. C. / H. P. F.; prostatic secretion normal	
W. B. 9	2/13/37	Urethral irrigations; prostatic massage; sitz baths; ice caps	3/27/37	Left, acute epididymitis; right, subacute epididymitis; subacute prostatitis and cystitis	In 3 days left epididymitis was one half former; painless; no nocturia or burning; 2d and 3d glasses clear; 1st glass hazy with shreds	3	0	14	Burning stopped in 2 days; urethral discharge minimal but still present in 12 days	Glasses 1, 2, 3 clear, rare shred in glass 1; glass 2 shows 1-2 W. B. C. / H. P. F.; prostatic secretion shows 6-8 W. B. C. / H. P. F.; asymptomatic
C. M. 10	3/26/37	None	3/30/37	Acute anterior urethritis	Burning stopped in 2 days; urethral discharge minimal but still present in 12 days	..	0	11	Smear positive for gonococci; glass 1 cloudy with shreds, glass 2 clear; asymptomatic	
C. W. 11	3/27/37	One urethral injection, strong $K_2MnO_4$	3/30/37	Acute anterior urethritis	Burning immediately improved; urethral discharge disappeared in 7 days	..	Lassitude and dizziness	11	Glasses 1, 2, 3 clear, shreds in glass 1; smear positive for gonococci; occasional "morning drop"	
H. C. 12	1926	Sounds, irrigations; prostatic massage, vaccine	3/30/37	Chronic anterior and posterior urethritis; chronic cystitis and prostatitis; urethral stricture	Urethral discharge stopped in 1 day; frequency stopped in 5 days	2	0	11	Glasses 1, 2, 3 clear, few shreds in glass 1; prostatic secretion normal; nocturia 1 time; occasional "morning drop"	
E. B. 13	3/16/37	Oral medication; urethral irrigations	3/30/37	Acute anterior and posterior urethritis	Urethral discharge and burning stopped in 1 day; frequency and nocturia stopped in 4 days	2	Methemoglobinemia fever (1 day)	11	Glasses 1, 2, 3 clear; no shreds; asymptomatic; reaction disappeared in 1 day	Last sulfanilamide on 4/7/37
A. R. 14	3/27/37	None	3/31/37	Acute anterior urethritis	Urethral discharge, burning, nocturia stopped in 7 days	2	Slight dizziness	9	Glasses 1, 2, 3 clear, 1 shred in glass 1; "morning drop"; asymptomatic	
J. S. 15	3/27/37	None	3/31/37	Acute anterior urethritis; pulmonary tuberculosis	Burning, nocturia stopped in 8 days; urethral discharge minimal, but present in 10 days	..	0	10	Glasses 1, 2, 3 clear, shreds in glass 1; minimal urethral discharge; positive for gonococci; asymptomatic	
C. M. 16	3/21/37	None	4/ 2/37	Acute anterior and posterior urethritis; acute inguinal adenitis	Urethral discharge, burning, nocturia stopped in 1 day; inguinal pain stopped in 2 days	2	0	8	Glasses 1, 2, 3 clear, 1 shred in glass 1; prostatic secretion normal (2 times); asymptomatic	
H. W. 17	4/ 4/37	Pyridium, urethral irrigations	4/ 6/37	Acute anterior and posterior urethritis; acute inguinal adenitis	Urethral discharge and burning stopped in 2 days	4	Slight dizziness	4	Asymptomatic; glasses 1, 2, 3 clear; rare shred in glass 1; glass 2 shows no W. B. C.	
J. G. 18	3/27/37	None	4/ 3/37	Acute anterior urethritis	Urethral discharge and burning stopped in 2 days	5	0	5	Nocturia 3 times, otherwise asymptomatic; glasses 1, 2, 3 clear	
A. S. 19	3/ 1/37	None	4/ 5/37	Subacute anterior and posterior urethritis; subacute prostatitis and seminal vesiculitis	Urethral discharge, frequency and burning stopped in 2 days	2	0	6	Asymptomatic; glasses 1, 2, 3 clear; many shreds in glass 1; prostatic and seminal vesicles not tender; prostatic secretion shows moderate amount of pus	No gonococci demonstrated after date of prostate and seminal negative smear

\* Since the paper was sent for publication, twenty-eight additional cases (to May 12) have been examined and placed under treatment as outlined. In summary to date, then, we have had forty-seven cases of various types of gonococcal infection of the genito-urinary tract. In thirty-six cases the gonococci and the urethral discharge disappeared in less than five days. In five cases the subjective symptoms disappeared completely; there was a marked diminution in the amount of the urethral discharge, but the gonococci were still present. In three cases there was no demonstrable response to the drug in that the symptoms persisted, there was no diminution of the discharge and many gonococci were present. In three cases there was a prompt response to the drug, but as treatment

was discontinued there was a recurrence of the infection. In two of these cases the infection disappeared following a second course of sulfanilamide. The most striking feature of our experience with these forty-seven cases has been that in no instance has there been a progression of the infection, even in the cases which showed no response to treatment. We realize that these cases have not been followed over a long period of time and in some instances the individual patients have failed to return for check up, so that the possibility of late recurrence in at least some of these patients cannot be definitely excluded. In the patients who have returned for check up, however, there has been no recurrence, except in the three instances mentioned.

out that infection with the hemolytic streptococcus, or changes brought about by the infection (probably a chemical reduction), is necessary for the activation of sulfonamide against the organism. Nineteen cases of beta hemolytic streptococcus infection of various types treated with these drugs are reported with dramatic improvement in the majority of cases.

In 1936 Buttle and his co-workers<sup>3</sup> in connection with Proom reported that sulfanilamide exerted a marked protective action against meningococcal infection in mice. More recently, Proom<sup>4</sup> has reported his results and states that "in mice infected with a suspension of meningococci in mucin, Prontylin protects up to one million lethal doses under optimum conditions." Schwenker,<sup>5</sup> in a recent report, presents a series of eleven cases of clinical meningococcal infection with sulfanilamide in which there was one death. He concludes that the treatment is as effective as that with antimeningococcal serum.

Marshall<sup>6</sup> has devised a simple and accurate method for quantitative determination of the amount of sulfanilamide present in the blood, urine and other body fluids and has pointed out much about its fate in the body. He shows that it is rapidly absorbed from the gastro-intestinal tract, enters practically all the body fluids and is excreted rapidly and almost entirely by the urinary tract both in unchanged form and conjugated with an acetyl radical. Retention of the drug in the blood occurs in cases of renal impairment.

Justina H. Hill<sup>7</sup> has found that the urine of patients excreting sulfanilamide has no bactericidal activity against beta hemolytic streptococci.

Sulfanilamide is relatively nontoxic, some patients tolerating 1 Gm. for 20 pounds (9 Kg.) of body weight daily for as long as a month without serious ill effects. A feeling of lassitude and dizziness is not uncommon during treatment. Colebrook reports several cases of sulfhemoglobinemia, which occurred in cases in which saline cathartics were given during administration of Prontosil. Sporadic cases of leukopenia have occurred, but none of these have been directly attributable to the drug. Acidosis, fever or a condition resembling methemoglobinemia may occur but are quickly relieved by appropriate therapy or reduction in dosage. While no serious toxic effects have been reported, it is obvious that patients must be kept under close medical observation during treatment.

The close biologic relationship between the meningococcus and the gonococcus is well known. It is difficult, however, to infect experimental animals with the gonococcus. It was therefore suggested to us by Dr. Perrin Long that the effect of sulfanilamide on clinical gonococcal infections be investigated directly without preliminary animal experimentation. An analysis of the result of oral administration of sulfanilamide in nineteen cases of gonococcal infection seen in the Brady Urological Dispensary of the Johns Hopkins Hospital is the basis of this report.

#### CLINICAL INVESTIGATION

*Diagnosis.*—The diagnosis of gonococcal infection was made on the demonstration of gram-negative intra-

cellular diplococci of typical morphology and distribution in the stained smear of urethral discharge or of the sediment from centrifugated urine. The smear was examined in practically all cases by two observers, and, in case of disagreement, cultures for the gonococcus were made. The diagnosis of posterior urethritis and cystitis were made by a correlation of the symptoms and the results of the three glass test. In some cases a diagnosis of acute or subacute prostatitis was possible on rectal palpation. A few patients were known to have had a chronic prostatitis before treatment was started.

*Treatment.*—With a few exceptions, all patients received, in four divided doses a day, 4.8 Gm. of sulfanilamide daily for two days, 3.6 Gm. daily for three days, and then 2.4 Gm. daily for from four to eight days. No other treatment, either local or general, was used. Fluids were not forced, as it was thought that this would hasten the elimination of the drug. Alcohol and sexual activity were prohibited. The patients were seen every two or three days during treatment, with few exceptions. Careful examination of the urine for pus and organisms was made on each visit. Cultures for gonococci and stained smears from the fossa navicularis were done whenever indicated.

The accompanying table briefly summarizes the results of examination and the clinical course of all our cases of gonococcal infection that have been followed for five days or more after beginning treatment with sulfanilamide.

There are, for analysis, nineteen cases of gonococcal infection which have been treated with sulfanilamide. Of these, the active urethral discharge disappeared in three cases in one day, in seven cases in two days, in two cases in three days, in two cases in seven days. In one case it disappeared in four days to recur slightly on the fourteenth day and again disappeared on the sixteenth day. One patient was treated for two days with sulfanilamide but failed to return until three days later, during which time no treatment was taken. The discharge had continued during this time. The drug was again administered for two days but the patient did not return until the twentieth day, at which time the discharge was still present and positive for gonococci. The drug was again administered and the discharge disappeared and the smear became negative for gonococci in the ensuing three days and has not recurred to date. The patient has now been seen twenty-four days since the treatment was discontinued; there is no discharge present and the urine is clear. In two cases the discharge is still present ten and twelve days respectively after the beginning of treatment. One patient, with chronic anterior and posterior urethritis, subacute prostatitis, subacute right epididymitis and acute left epididymitis had no urethral discharge, but gonococci were demonstrated on smear and culture from the urine. The organisms disappeared three days after the institution of treatment, and there had been marked diminution in the swelling of the left epididymis. The urine was hazy in the first glass, the second and third glasses were clear, and the patient's symptoms had disappeared. When seen last on the fourteenth day after the institution of the treatment, the patient was free from symptoms, there was no urethral discharge and the urine was clear in three glasses. Prostatic secretion showed from 6 to 8 white cells per high power field.

Stained smears from the urethral discharge and centrifugated urine became negative for gonococci (to date) in five cases in two days, in five cases in three

3. Buttle, G. A. H.; Gray, W. H., and Stevenson, Dora: Protection of Mice Against Streptococcus and Other Infections by Para-Aminobenzenesulfonamide and Related Substances, *Lancet* **1**:1286 (June 6) 1936.

4. Proom, H.: Therapeutic Action of Para-Aminobenzenesulfonamide in Meningococcal Infection of Mice, *Lancet* **1**:16 (Jan. 2) 1937.

5. Schwenker, Gelman and Long: Treatment of Meningococcal Meningitis with Sulfanilamide, to be published.

6. Marshall, E. K., Jr.; Emerson, Kendall, Jr., and Cutting, W. C.: Para-Aminobenzenesulfonamide, *J. A. M. A.* **108**:953 (March 20) 1937.

7. Hill, Justina H.: Personal communication to the authors.

days, in two cases in five days, and in one case each in four, six and twenty-three days. In one case smears became negative on the ninth day, positive on the fourteenth day and again negative on the seventeenth day. In three cases gonococci are still present after eleven days.

Symptoms of burning and frequency disappeared in two cases in one day, in eight cases in two days, in two cases in three days, and in one case each in four, five, seven and eight days. There is no note on the history in three cases.

Symptoms of slight dizziness and lassitude occurred in four cases with the initial larger doses but disappeared when the amount of the drug was reduced. One patient had fever, general malaise and sulfhemoglobinemia for two days, but these symptoms disappeared within twenty-four hours after medication was discontinued.

Two patients with known preexisting chronic prostatitis and two patients with subacute prostatitis were found to have a normal prostatic secretion after treatment for from ten to twelve days. In three other cases of subacute prostatitis at the beginning of treatment, one subsequently showed from 6 to 8 white blood cells per high power field, one showed a few clumps of pus, and in the third the pus was only slightly reduced in six days.

In several instances it was noted that, as the urethral discharge began to disappear, the gonococci were found to lie extracellularly, with little or no evidence of phagocytosis by the leukocytes.

Five or six of the cases showed a much slower response to the administration of sulfanilamide than did the others, and we felt that three or four were little if any benefited by the drug. The reason for such failures is not clear. One of the patients had a very small amount of the drug during the first five days and another did not return for fifteen days during the early treatment. The others of this group were quite conscientious in attending the clinic and obeying instructions. Estimations of the concentration of sulfanilamide in the blood have not been made on these patients. It is possible that some abnormality in the metabolism of sulfanilamide in these particular individuals may explain some of the failures.

The use of sulfanilamide in gonococcal infections is as yet in an entirely experimental state. Nevertheless the surprisingly prompt response to treatment in the majority of our cases has deeply impressed all those who have seen them. The prompt disappearance of urethral discharge and symptoms of burning and frequency have been most striking, especially when contrasted with the clinical course of patients treated with the usual methods heretofore in use. It has been especially impressive to us that the infection in none of our treated cases has progressed from anterior to posterior urethritis or from posterior urethritis to prostatitis or epididymitis after the institution of the treatment.

While only one of our cases in which the discharge had been absent for a period of a week has shown a recurrence of the infection, it must be realized that larger series of cases must be followed over a longer period of time before a complete evaluation of sulfanilamide in the treatment of gonococcal infections can be determined. Further studies must also be made to determine the optimum dosage and the length of time during which treatment should be continued.

An emphatic warning should be sounded as to the possibility of reactions from this drug, as should be done of course in the clinical use of any new drug or treatment. Immediately on the complaint by the patient of lassitude or dizziness, the dosage must be reduced or the drug discontinued completely. We have observed no serious symptoms. Should symptoms persist, a complete blood study should be done.

Our relatively brief experience with the use of sulfanilamide in the treatment of gonococcal infections has led us to believe that this drug will prove of great value. The prompt response to treatment in the vast majority of our cases, the smooth clinical course, the fact that no complications have occurred and that the infection has not progressed, together with the reduction in hospital expenses from the use of the necessary drugs and medicaments previously used in the treatment of this type of infection, have impressed us profoundly. This preliminary report is therefore presented for the purpose of stimulating the careful use of this drug in clinics where large numbers of gonococcal infections can be closely followed, so that an accurate evaluation of sulfanilamide in the treatment of gonococcal infections can be determined and the optimum dosage and possible deleterious effects further studied.

## EXPERIMENTAL STUDIES WITH SULFANILAMIDE AND WITH PRONTOSIL

IN HEMOLYTIC STREPTOCOCCUS INFECTIONS

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The results obtained by the use of sulfanilamide and of prontosil<sup>1</sup> in the treatment of infections produced by hemolytic streptococci,<sup>2</sup> and, to a lesser degree, of infections produced by type III pneumococci,<sup>3</sup> leave no doubt as to the therapeutic efficacy of these compounds; but at the same time an adequate explanation of the mechanism of their action is lacking.

Colebrook, Buttle and O'Meara<sup>4</sup> found sulfanilamide to be bactericidal against the hemolytic streptococcus *in vitro* and, to a limited degree, *in vivo*. They also recognized a discrepancy between the remarkable therapeutic results obtained and the limited bactericidal activity observed and suggested that the enhanced bactericidal action of the drug was supplemented by that of the tissues of the whole animal. Long and Bliss,<sup>5</sup> on the other hand, considered the stimulation of phagocytic activity of the polymorphonuclear leukocytes and of the monocytes of paramount importance in the mechanism of action of these drugs.

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1. In this paper prontosil refers to the disodium salt of 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene-3', 6' disulfonic acid, is a product of Winthrop Chemical Company.

2. The literature has been listed by Long, P. H., and Bliss, Eleanor A.: Para-Aminobenzenesulfonamide and Its Derivatives, *Arch. Surg.* **34**: 351 (Feb.) 1937.

3. Rosenthal, S. M.: *Pub. Health Rep.* **52**: 48 (Jan. 8) 1937. Cooper, F. B.; Gross, Paul, and Mellon, R. R.: *Proc. Soc. Exper. Biol. & Med.* **36**: 148 (March) 1937. Gross, Paul, and Cooper, F. B., *ibid.* **36**: 225 (March) 1937.

4. Colebrook, Leonard; Buttle, G. A. H., and O'Meara, R. A. Q.: *Lancet* **2**: 1323 (Dec. 5) 1936.

5. Long, P. H., and Bliss, Eleanor A.: Para-Aminobenzenesulfonamide and Its Derivatives, *J. A. M. A.* **108**: 32 (Jan. 2) 1937.