# SULFANILAMIDE IN THE TREATMENT OF GONORRHŒA

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DURING the past three years in Europe and during the past year in America a considerable number of reports have been published attesting the value of para-amino-benzene-sulfonamide in the treatment of hæmolytic streptococcal infections.[1] More recently it has been shown that it is also a potent chemotherapeutic agent in meningococcic infections.[2] The close relationship between the meningococcus and the gonococcus led Dr. Perrin H. Long, who has been a pioneer in America in the study of sulfanilamide, to suggest that it be given a trial in gonorrhœa. The first report was made recently by Dees and Colston[3] and their results were decidedly impressive. The purpose of this paper is to report the results in the sulfanilamide* (para-amino-benzene-sulfonamide) treatment of 134 patients with gonococcic infections of the genito-urinary tract treated in the Provincial Government Clinic, Edmonton.

## THE MODE OF ACTION OF SULFANILAMIDE

Long and Bliss[4] have shown that a 1:10,000 concentration of para-amino-benzene-sulfonamide in serum broth markedly inhibited the growth of alpha hæmolytic streptococci, gamma streptococci, pneumococcus types I and II, several varieties of Neisseria from the throat, *M. tetragenus, H. influenzæ* and *H. hæmolyticus.* The growth of *S. aureus, B. typhosus, B. paratyphosus A, B. para-typhosus B,* enteritides, Flexner, Shiga and several other Gram-negative bacilli, was not affected by this concentration of the chemical. This inhibition may also occur *in vivo,* but in addition to this effect of the drug it is felt that the microörganism must also be damaged to permit of a marked degree of phagocytosis by the leucocytes. On the other hand the experiments of Mellon, Gross and Cooper[5] showed no indication that phagocytosis is a factor in the mechanism of the therapeutic action of this drug, and this seems to be borne out by the fact that the pustular discharge in acute gonorrhœal urethritis begins to diminish about four hours after the ingestion of large doses of sulfanilamide. The question of the mode of action is therefore unsettled.

*Toxicity.* — All of our 134 adult patients tolerated 80 grains of sulfanilamide daily for four days without ill effect. It is known that some patients have tolerated ¾ of a grain per pound of body weight daily for a month without serious results. Six of our patients developed skin rashes during the period of maximum dosage. In all six the eruption occurred after exposure to sunlight and was confined to the hands and face, there being sharp lines of demarcation at the rim of the collar and the bottom of the sleeves. In four of the patients the eruption was urticarial, in one a mixture of urticaria and dermatitis, and in one dermatitis only. The urticaria cleared up within twenty-four hours after discontinuing the drug and did not recur when the medication was resumed with half the former dosage.

All of our patients were conscious of a drug effect, which varied from a slight feeling of dizziness or lassitude to a definite inability to do work which required mental concentration. Headache, when it occurred, was not severe. There were no cases of acidosis and only two of fever (routine temperatures were not taken). One patient developed a condition suggestive of methæmoglobinæmia, which disappeared in a few hours when the drug was stopped and did not recur when treatment was resumed with a smaller dosage. Complete blood counts have been done on more than one hundred of our patients and no changes attributable to the treatment have been noted. The gastric analysis in 8 of our failures showed normal acidity. No renal changes were noted. It should be borne in mind however that in case of renal impairment retention of the drug in the blood occurs.

* The para-aminobenzene-sulfonamide used in this series of cases was supplied by the Winthrop Chemical Company, under the trade names of "Prontylin", and "Prontosil"), and by the Lederle Laboratories ("Sulfanilamide").

In short it would appear from the study of the literature and from personal observation that sulfanilamide is relatively non-toxic.

*Absorption and excretion.*—Marshall, Emerson and Cutting[6] have shown that in the dog absorption from the gastro-intestinal tract is rapid, being usually complete or nearly complete in four hours. In patients when large amounts of sulfanilamide are administered daily in divided doses nearly 100 per cent may be recovered from the urine when equilibrium between intake and output is established. It takes from two to three days to establish this equilibrium and the same time to free the body of the drug after it is discontinued. Subcutaneous injection of the substance does not lead to higher blood concentration than when it is given by mouth. It passes readily into the tissues and is found in the cerebrospinal fluid in only slightly less concentration than in the blood. The optimum concentration in the blood stream is 1:10,000 and this is easily obtained by rather large initial doses of the drug and is maintained by considerably smaller doses. A method for determining the blood level has been described by these authors[6] and more recently a simpler and more sensitive modification has been described by Marshall.[7] The human subject excretes the drug partly unchanged and partly conjugated in the form of an acetylated derivative.

## CLINICAL OBSERVATIONS

Sulfanilamide treatment of 51 male patients was begun on May 15th, these being the ordinary clinic run of patients attending on that day, and no selection of patients was made. Some had resisted the ordinary clinic treatment for months, and the common complications of the disease were represented in this preliminary group, including 1 of acute prostatitis, 5 of chronic prostatitis, and 1 of epididymitis. From day to day additional cases were started on sulfanilamide, to bring the total of this series to 30 females and 104 males. The diagnosis of gonorrhœa was confirmed routinely in each case by the demonstration in the laboratory of typical intracellular diplococci in the methylene blue stained smear of the urethral discharge. In the females smears were also made from the cervix. This was checked by the independent examination of duplicate smears stained by Gram's method in the Provincial Laboratory. Of the 30 female cases in this series all had positive smears within the five days preceding the institution of the sulfanilamide treatment. All the patients were ambulatory except one with acute prostatitis.

Of the males the first 51 of the series varied as to the duration of the disease from one day to several months; the succeeding 53 cases were all recently acquired infections of from one to five days' duration and coming under treatment for the first time. In the entire series of 134 adult cases the treatment consisted of: (1) 80 grains of sulfanilamide daily for the first four days; 40 grains daily for the second four days and 20 grains daily for the next seven days. The daily dose was divided into four equal portions and given every four hours from 8.00 a.m. to 8.00 p.m. (2) Each patient was instructed to drink large quantities of water and of milk; all other fluids were prohibited. Other than this no instructions were given as to diet. (3) No local treatment of any kind was administered to any of these patients. Other patients treated in the clinic but who disappeared before completing the course, even though they appeared to be cured, have not been included in this series.

The cured patients have been followed for periods varying from one month to more than three months subsequent to the conclusion of the treatment. Relapses have occurred up to three weeks following an apparent cure, and although re-infection could not be ruled out these cases have been listed with our failures. Five of our uncured patients were placed in hospital, and for a period of five days were given prontosil subcutaneously in doses of 10 c.c. every four hours, or a total of 250 c.c. for each patient. In four of them the disease was not influenced by the treatment; the fifth case was very much improved but not cured. Our determination of a cure in the male was based on the absence of gross pus or shreds in the first and second glasses of urine and by the demonstration of not more than eight pus cells per oil-immersion field in the prostatic fluid; in the female by a series of not less than ten negative daily smears from the urethra and cervix.

Of our total of 134 cases 87.3 per cent were cured. Of the 104 males 91, or 87.5 per cent, were cured, 6 in one day, 13 in two days, 25 in three days, 14 in four days, 8 in five days and

25 in six to fifteen days; of the 30 females 26, or 86.6 per cent, were cured, but it is difficult in the females to decide just when the cure was effected. The females were seen and smears were made daily, some for as long as two months. In all cured cases the smears became negative within two weeks and symptoms of the disease disappeared. Of the 17 failures in this series not one seemed to be influenced by the drug. No complications whatever occurred in any of our patients during treatment.

One should approach the task of evaluating the curative effect of a new drug with an attitude of scepticism. Too often brilliant therapeutic successes have in the end proved to be due to optimism on the part of the observer. Many more cases will have to be observed over longer periods of time before a final decision can be reached, but the preliminary results would seem to indicate that sulfanilamide is of outstanding merit in the treatment of gonococcic infections.

## SUMMARY

1. Twenty-six, or 86.6 per cent, of 30 females and 91, or 87.5 per cent, of 104 males affected with gonorrhœa were cured within fifteen days by a course of treatment consisting solely of the oral administration of sulfanilamide and large quantities of fluids.

2. No complications occurred in any of the patients in this series subsequent to the commencement of sulfanilamide therapy.

3. The total dosage of sulfanilamide given to each patient was 620 grains during a period of fifteen days.

4. The drug sensitizes some patients to sunlight, which produces an acute urticarial eruption on the exposed skin.

## REFERENCES

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