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Sulfanilamide in the Treatment of Leprosy[1]

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The introduction of sulfanilamide as a potent chemotherapeutic agent for combating certain types of invasive bacterial diseases and the striking results obtained from its use have led to a widespread trial of the drug. Bacteriological experiments by Long and Bliss *(2)* tend to prove that sulfanilamide does not in itself kill the microorganisms but exerts a bacteriostatic effect which aids the normal defenses of the body in overcoming infection. The administration of sulfanilamide and related compounds has been associated with definite although not necessarily unavoidable or serious hazards. In a recent article, Long and his associates *(3)* analyzed the toxic manifestations which occurred during the course of treatment with this drug in one thousand cases at the Johns Hopkins Hospital. The most common toxic effects were headache, dizziness, nausea, vomiting, cyanosis, drug fever, and drug rashes. The most serious toxic manifestations, however, were those associated with the blood or hemopoietic system and the liver (hepatitis).

Impressed by the action of sulfanilamide on other diseases, the writers decided upon its experimental administration to combat secondary infection in

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leprosy. They also wished to see if it would have an influence on the disease itself if given over a sufficient period of time and in sufficient dosage to produce an effective blood level.

First course—At the beginning of the experiment nine patients, eight males and one female, were chosen from a group of volunteers. Eight of these cases were lepromatous and one was neural, although they all showed some neural manifestations.

Certain preliminary laboratory procedures were carried out in all cases. As a measure of kidney function, the urea clearance test was made, in addition to a complete urinalysis and estimations of the non-protein nitrogen and the urea nitrogen of the blood. A complete blood picture was made, this including the erythrocyte count, hemoglobin estimation (Sahli's method), total and differential leukocyte counts, and the sedimentation test (Cutler's method). Because of the toxic effect of the drug on the hemopoietic system, the determination of the blood elements was repeated every second day during the course of the treatment, and in some instances every day. Urinalyses were also made frequently. Patients with markedly impaired renal function were not chosen, because sulfanilamide is largely excreted by the kidneys and its accumulation in the body would give rise to toxic manifestations.

Long and Bliss consider 4 to 8 mg. percent of sulfanilamide an effective blood level in patients with mild or moderately severe tissue infection, and 10 to 15 mg. percent in patients who are severely ill. The plan adopted at the outset was to give 15 grains (about 1 gm.) of sulfanilamide and 15 grains of sodium bicarbonate at 4-hour intervals, four times daily for 6 days, then the same doses twice daily for 6 weeks. With this dosage the free sulfanilamide concentration of the blood ranged between 5.5 and 16.6 mg. percent, with an average of 9.0 mg.

Only two of these patients completed the 6-week course of treatment without toxic manifestations. The other seven were all hospitalized for fever ranging from 38° to 41° C. and other toxic disturbances. In these cases the treatment had to be discontinued between the sixth and the twenty-first days because of the following complications: drug fever, 4; neuritis, 1; drug dermatitis, 1; and hepatitis, 1. The amount of sulfanilamide taken by thee patients varied from 315 to 1,650 grains (20 to 105 gm.).

One of these patients was critically ill. Jaundice was noted on the sixth day, and it was felt that a toxic hepatitis was developing. The liver and spleen were palpably enlarged. The icteric index was 50 units. The free sulfanilamide blood concentration was 16.6 mg. percent, and that of nonprotein nitrogen was 40 mg. percent. The drug was discontinued. Three days later the patient became delirious and the surface of the body was cold and clammy. Dextrose, 5 percent in physiologic saline, was administered by vein and subcutaneously, and the patient improved. Two weeks later the icteric index was 20 units. Within 1 month the weight increased 23 pounds and was maintained.

Second course—After a rest period of 2 months, a second series of treatments was given to 6 of the above group and also to an additional 11 patients, 11 males and 6 females. This made a total of 20 patients who received sulfanilamide therapy, 14 taking one course and 6 taking two courses. Those taking the second course included 1 neural case and 16 active lepromatous ones which varied in degree of the disease from early to advanced.

The same laboratory analyses as before were carried out on this group before initiating treatment, but the subsequent examinations were made twice a week instead of every second day, unless it became necessary to do so more often. Because of the severe toxic reactions experienced in the first group, it was thought advisable to decrease the dose of the drug for the second course. The plan adopted was to try to obtain a sulfanilamide blood level between 4 and 8 mg. percent. To maintain this level, 15 grains of sulfanilamide and 15 grains of sodium bicarbonate were given at 4-hour intervals, four times daily for 2 days, after which the dose was lowered to 10 grains of each drug, three times a day for 12 weeks. The free sulfanilamide concentration of the blood of these patients was found to range between 3.2 and 9.0 mg. percent, with an average of 5.0 mg.

In this series the total number of days of treatment ranged from 3 to 92, and the total dosage varied from 75 to 2,880 grains (5 to 190 gm.). Six of the patients completed the entire course. It was necessary to hospitalize 12 of the group because of toxic reactions or fever, and the medication was discontinued in 11 of them. In spite of a continuous fever for more than a week, during which time the evening dose of the drug was omitted, the other case was able to complete the course of 88 days of treatment without further ill effects.

Altogether the drug had to be discontinued on account of high continuous fever in six cases. In one case progressive anemia was the reason for interrupting the treatment; in another it was persistent neuritis, and in still another, recurrent hepatitis.

One case suffered from cerebral depression followed by semicoma after the sixteenth day of treatment. She became critically ill, with a temperature of 40° C. and a leukocyte count of 50,200 per cmm., with 94 percent neutrophiles (37 staff cells and 57 segmented cells). The blood nonprotein nitrogen was 50 mg. percent; the urine was negative for albumin, sugar, blood, and casts. After discontinuing the drug, 1,000 cc. of 5 percent dextrose in physiologic saline was given introvenously, two such doses being administered 6 hours apart. Two days later the patient was markedly improved.

Another case developed a rash over the entire body, and treatment was discontinued. After several weeks the treatment was resumed and the rash recurred, indicating that the dermatitis was probably due to the drug.

SUMMARY OF LABORATORY DATA

No severe blood dyscrasia, such as granulocytopoenia or severe hemolytic anemia, was experienced among the group treated.

Anemia—Examinations of the average erythrocyte and hemoglobin levels showed, over a period of 80 days, a slow progressive drop in all cases. While in the majority of instances this anemia was mild, a significant decline up to 50 percent was not an unusual finding. In three cases, the drug was discontinued because of slow progressive anemia. The erythrocytes dropped from 4,100,000 to 1,970,000 per cmm. in 34 days in one of them, and from 3,790,000 to 2,100,000 in 40 days in another, while the hemoglobin fell from 84 to 48 percent in 78 days in the third.

Leukocytosis—The persistence of leukocytosis of 12,000 per cmm. or more occurred in 14 of the cases, in whom 138 high counts were recorded. The figures averaged between 12,000 and 25,000. One case had a count of 50,200, and another had 40,300.

Leukopenia—Leukopenia was considered to be present when the leukocyte count fell to a level below 5,000. Of the 20 patients, depression of the leukocytes below this level occurred in 6, for whom 27 low counts were recorded. In only 2 of the cases was the leukocyte depression noted more than once. The lowest count was 3,700.

Differential count—Detailed examination of the leukocytes revealed significant changes in the neutrophiles and eosinophiles. All cases but one showed a shift to the left (Shilling's hemogram), whether they had leukopenia or leukocytosis. In 5 of those with leukopenia, myelocytes were noted once and juveniles in 17 instances.

Eosinophilia (5 to 23 percent) occurred in 12 of the cases and was found on from 1 to 19 occasions in each case, with a total of 65 times. Only 1 case had eosinophilia (7 percent) before treatment was started. On admittance the feces examination was negative for ova and worms, and no other cause for the eosinophilia was found. It is significant that it was this patient who developed the highest eosinophilia (23 percent) during the treatment.

Eosinophilia has not been reported in the literature as a result of treatment with sulfanilamide or related compounds. The reason for the increae in these cells in about one-half of the leprosy patients so treated is unknown. It is interesting that the two patients who developed severe drug rashes did not show eosinophilia, so that dermatitis was not the exciting factor. The acute leprous skin reactions noted in several of the cases also did not seem to account for it. Might not the appearance of eosinophiles in the blood stream in such large numbers in a chronic disease like leprosy indicate a favorable tissue reaction to the disease?

COMMENT ON COMPLICATIONS

On the whole, the toxic complications of sulfanilamide therapy in leprosy seemed to be more frequent and more severe than those reported in the literature as occurring in the treatment of other infectious diseases *(1)*. The initiation of acute lepra reaction was not an unusual occurrence; it was noted in 9 of the cases treated. Drug fever was observed in 12 of the patients (60 percent). At times it was difficult to determine whether the patient's fever was due to toxicity of the drug or to the setting up of a lepra reaction by the drug. Neuritis was a complicating factor in 4 patients, whether caused by the drug directly or due to its stirring up of a lepra reaction in the nerve. Conjunctivitis was noted in 3 patients, and a drug dermatitis in 2. Finally, the changes produced in the blood pictures of all the patients, as noted above, seemed to be a rather unusual and sever type of reaction.

RESULTS OF THE TREATMENT

Of the entire group of 20 patients treated, 6 show some improvement of their leprous lesions. Two others show improvement, but they were improving when the treatment was started. One is probably stationary. The remaining 10 show probably slight progression of the disease. In 2 of the cases the sulfanilamide treatment definitely helped to clear up secondary infections. It is of interest in this connection that sulfanilamide therapy produced prompt improvement of pseudoerysipelas in 12 patients not included in this group. One patient of the treated group has since died of ovarian carcinoma, with no change in the leprotic condition.

CONCLUSIONS

Sulfanilamide therapy has proved effective in the treatment of secondary infections complicating leprosy, and as a help in the healing of secondarily infected leprous ulcerations.

Sulfanilamide cannot be regarded as a curative agent for leprous lesions, either of the macular or lepromatous type.

The significance of the development of eosinophilia during the course of sulfanilamide treatment is interesting and may be a fruitful field for future study.

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