THE CHEMOTHERAPY OF PNEUMONIA

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The introduction of sulfanilamide as a therapeutic agent caused a tremendous increase in interest in the subject of chemotherapy generally and following the demonstration of its success against the hemolytic streptococcus, it was tried extensively in pneumococcal infections. A considerable degree of therapeutic success was obtained but its value was somewhat lessened by the severe toxic effect. Efforts were then made to produce related compounds of lessened toxicity. In May, 1938, Whitby[1] published his results in protection of mice from experimental pneumococcal infections with a new compound first labeled M & B 693 or dagenan, which has come to be known in this country as sulfapyridine. Chemically it is 2- (P-aminobenzenesulphonamido) pyridine. Whitby demonstrated that this compound was of low toxicity and would protect mice against 10,000 lethal doses of Type I pneumococcus and that it would afford a high degree of protection against infection with Types II, III, V, and VIII pneumococci.

Evans and Gaisford[2] reported the results of a study of 100 cases of pneumococcal pneumonia treated with this compound in July, 1938. They recorded a mortality rate of 8 per cent in a group of cases treated with this material as against 27 per cent in a control group of 100 cases receiving nonspecific treatment. This remarkable advance in the therapy of a difficult infection attracted widespread attention and has now been confirmed by numerous investigators[3, 4, 5] whose reports show that the average mortality figures have been reduced from the usual 25 to 30 per cent to figures ranging from 3 to 11 per cent.

The present report is an attempt to evaluate the success of sulfanilamide and sulfapyridine therapy at the Cleveland Clinic since the introduction of each of the drugs in all pneumonias, whether of the lobar or bronchopneumonic type. Sulfanilamide was used in these cases from the time it became available until the early months of 1939 when sulfapyridine was introduced. There were altogether forty cases, with a diagnosis in twenty-seven of bronchopneumonia, and in thirteen of lobar pneumonia. Of the bronchopneumonia, it was considered that only six represented an uncomplicated, pulmonary infection, the others being patients with severe, pre-existing disease. In the majority of this latter group, it is apparent that conditions apart from the lung form the primary difficulty, the pneumonia being in many instances purely terminal. In some of these complicated bronchopneumonia cases, death was inevitable from other conditions, but for the sake of completeness, they have been included in this study. Of fourteen cases of bronchopneumonia treated with sulfanilamide, there were three recoveries and eleven deaths. Of these cases, only two were considered to be uncomplicated broncho-

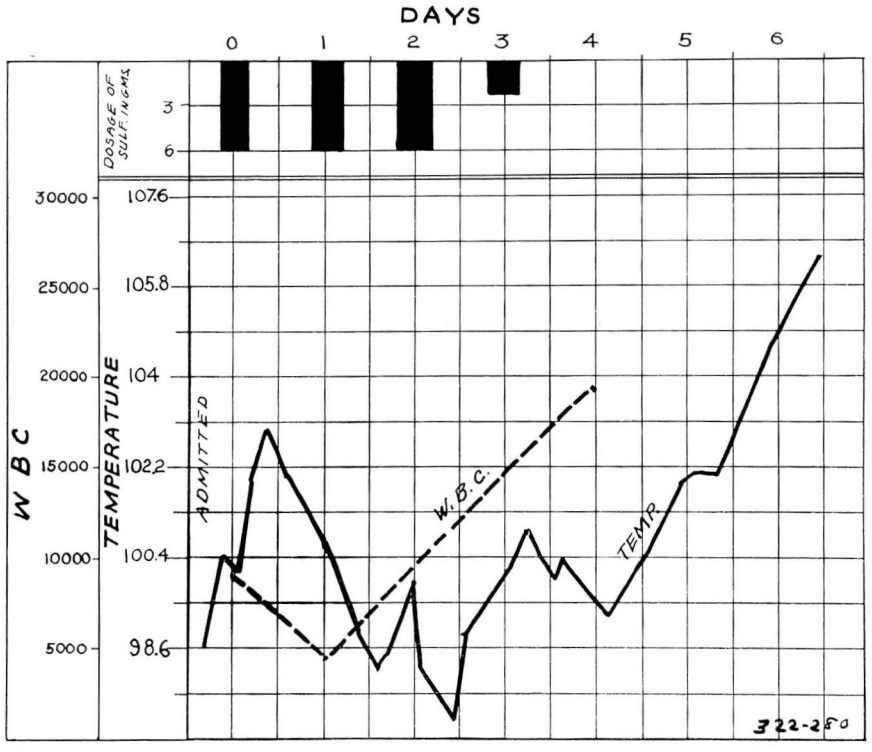

FIGURE 1: Graphic chart of Case 1. Sulfapyridine levels were not obtained.

pneumonia and both recovered. There were thirteen bronchopneumonias treated by sulfapyridine, with seven recoveries and six deaths. Of this group, four were considered to be uncomplicated cases of bronchopneumonia and all recovered. In the lobar pneumonia group, there was one case treated with sulfanilamide with recovery and twelve cases treated with sulfapyridine with ten recoveries.

Sputum examinations in the bronchopneumonia group showed a variety of organisms with the streptococcus predominating, whereas the pneumococcal group showed Types III, VI, VIII, XIV and XIX. Types I and II were not represented and the type was not determined in four cases.

The *dosage* of sulfanilamide used varied considerably with the clinical findings. On the average, approximately 20 grains was given every four hours, day and night, during the first two days, with a reduction thereafter of the dosage to 15 or 10 grains every four hours, depending upon the blood concentration, the level being checked each morning. A therapeutic level of between 10 and 15 mg. per 100 cc. was regarded as being of maximum therapeutic efficiency, and the dosage was varied in individual instances to secure this level. In the cases treated with sulfapyridine, the usual initial dosage was 2 grams followed by 1 gram every four hours day and night. Daily blood estimations were made in an

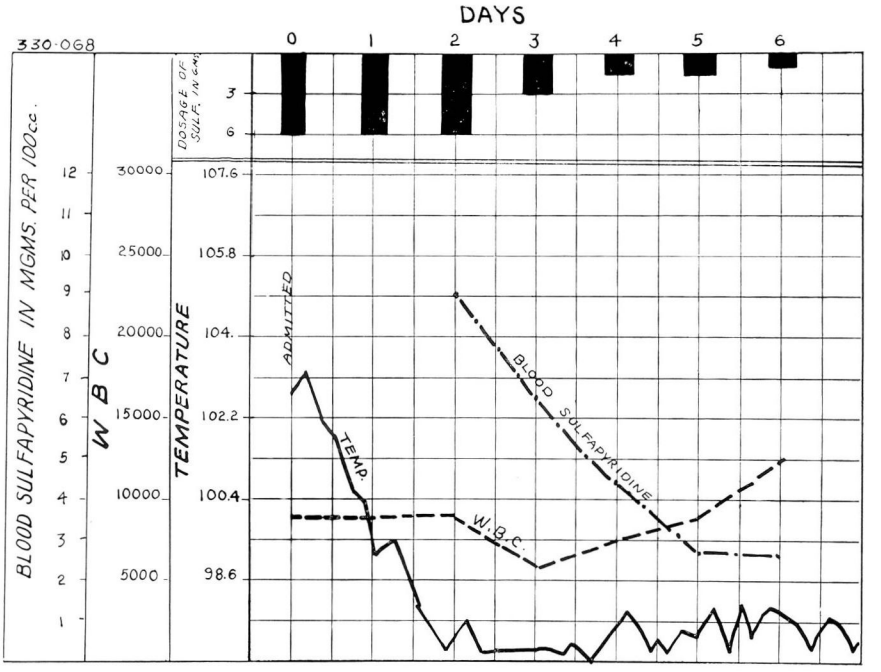

FIGURE 2: Graphic chart of Case 3.

attempt to maintain the level at between 5 and 10 mg. per 100 cc. Therapy was maintained at this level when possible, for at least two days after the patient was temperature-free; then the dosage was reduced gradually. The total dosage varied between a lower limit of 20 grams to an upper limit of 66 grams in one instance. Sodium sulfapyridine monohydrate was not used in this series. It was very evident that the concentration of the drug in the blood stream varied greatly in different patients on the same dosage. Particularly in the patient with renal failure it was found that the concentration of the drug tends to increase rapidly, whereas in other instances, even with large doses of the drug, it was impossible to raise the blood level to the desired limit, apparently due to a failure of absorption. Thus, in one instance of Type XIX pneumococcal pneumonia, a blood sulfapyridine level of 4.5 mg. per 100 cc. was the maximum attained on the above medication and rapidly fell off when the dosage was reduced in accordance with clinical improvement to levels of 1.8 mg. and 1.2 mg. per 100 cc. In another instance on the above mentioned dosage, the blood level reached 9 mg. on the morning of the second day and was maintained at a level averaging 6 mg. per 100 cc., even with reduction of the oral dosage. This patient had a heavy albuminuria on his admission which cleared up within three days of his hospital entrance.

It is difficult to see that the effects of sulfanilamide or sulfapyridine

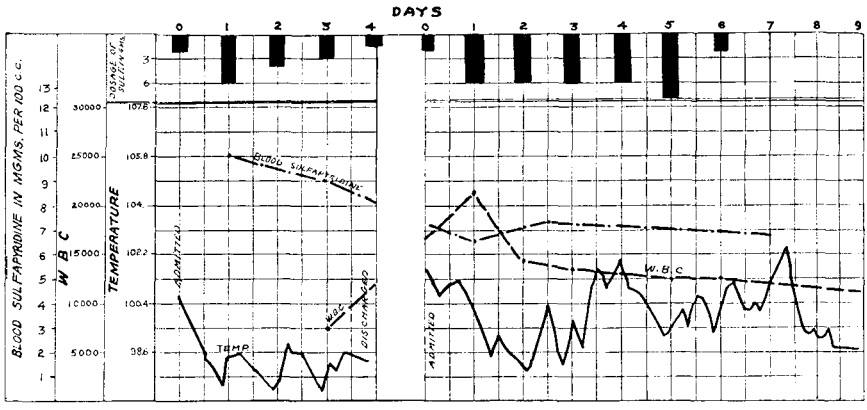

FIGURE 3: Graphic chart of Case 4.

have affected the clinical course of the complicated bronchopneumonia group. As stated above, it is our opinion that the bronchopneumonia was merely an expression of their terminal condition. In those complicated bronchopneumonias with extra pulmonary conditions not necessarily immediately fatal, it was our clinical impression that the effects of the drug were distinctly beneficial. In the uncomplicated bronchopneumonias, a rapid reduction of temperature was accomplished with both sulfanilamide and sulfapyridine, the effect being somewhat more striking with the latter. The reduction of temperature to normal and its maintenance at a normal level was not as striking, however, in this group as was the result in the lobar pneumonias—to be discussed later. Frequently some recurrence of temperature was noted, suggesting some flare-up of the lesion, but in general the results of therapy have been reassuring and suggest that in the various bronchopneumonias of indeterminate origin, a trial of this therapy is indicated.

In regard to the *lobar pneumonia*, the striking finding has been a *rapid reduction in temperature*, usually to normal, within a period of twenty-four to thirty-six hours. This has been such a constant feature that its nonappearance suggests either inadequate therapy or the presence of a pneumonia of other than pneumococcal origin. In several instances the temperature has remained normal from that time on, whereas at times there have been slight recurrences of fever within the next few days. In some instances this has been due to insufficient dosage with an increase in the pulmonary lesion. In a few instances it has been caused by a specific drug fever. It may at times be difficult to distinguish between the two causes. An increasing temperature after three or four days of treatment in the face of apparently adequate therapy suggests the possibility of drug fever. A decreasing white blood count even to the point of leukopenia also suggests the drug basis for fever whereas an increasing leukocytosis is suggestive of a spread of the pulmonary lesion. Withdrawal

of the drug causes cessation of the specific drug fever within a few hours. It is interesting to note that despite the increase in well-being felt by the patient, and the favorable temperature chart, the pulmonary process apparently goes through its normal stages of congestion and hepatization with final resolution in the usual fashion, although it would appear that these processes are somewhat accelerated. In general it would appear that a beneficial effect can be readily noted within a three-day period, if it is going to occur.

Symptomatically, the effect of sulfapyridine therapy may be very striking. Headache, malaise and restlessness which are commonly seen at the beginning of treatment tend to subside within the first two days and may be replaced by the lassitude which is commonly seen when the drug is administered. There would appear to be some slowing up of mental processes and the apprehension frequently seen in these patients is distinctly lessened. With the reduction in fever, the fluid loss in perspiration is greatly reduced and the necessity for the administration of large quantities of fluids becomes lessened.

The *incidence of toxic manifestations* with both sulfanilamide and sulfapyridine therapy has been relatively small. With both drugs most of the patients experience nausea within a few hours and in about one-third of the cases actual vomiting occurs. This is somewhat more likely to occur with sulfanilamide than with sulfapyridine and, particularly with sulfanilamide, nausea may be decreased by the use of equal amounts of sodium bicarbonate. It has been amply demonstrated that the nausea and vomiting of themselves do not constitute an indication for stopping the drug, since persistent use of the drug may result in marked lessening or disappearance of this symptom. Dosage lost in this way should be replaced immediately. It was found that crushing the tablet will frequently tend to reduce this effect, and dissolving the medication in orange juice or milk or dividing it into small doses every hour may be effectual. Occasionally the vomiting may be reduced by the use of simple sedatives, and in a few cases we found it necessary to administer glucose and saline intravenously to combat fluid loss. Cyanosis is present in practically all patients to some degree although it is somewhat questionable what part of this is due to the drug itself in a disease characterized frequently by cyanosis. A drug eruption was noted in two patients and definite drug fever appeared in one patient. A few red blood cells were noted in the urine in three cases, but gross hematuria and ureteral colic were lacking in our series. A mild hypochromic anemia developed in three patients; granulocytopenia was not seen in any case.

The essential findings in the two fatal cases were as follows:

Case 1: A sixty-four year old man was admitted with pneumonia of the right lower lobe. Type XIV pneumococcus was demonstrated in the sputum. *Other laboratory findings* showed a two plus albuminuria, a blood urea of 111 mg.

per 100 cc. and a white blood cell count of 9,600 with 98 per cent neutrophils. On routine sulfapyridine therapy there was an initial decrease in temperature to normal for one day, then the temperature began to rise again and continued upward despite sulfapyridine therapy. The white blood cell count rose to 18,000 and the blood urea rose to 144 mg. per 100 cc., despite adequate fluids. The patient died six days after treatment was started, with renal failure probably playing a large part in this outcome.

Case 2: A seventy-two year old man was admitted with evidence of pneumonia involving the lower two-thirds of the left lung. There was some question of involvement of the right base. Type VI pneumococcus was isolated from the sputum and 100,000 units of Type VI antipneumococcus serum was given with 8 grams of sulfapyridine in the first twenty-four hours. Subsequent sputum examination revealed the presence of a Type III pneumococcus and another 100,000 units of serum was given. The blood culture was negative. The white blood cell count was reported as 5,950; it gradually rose to 12,000 but then dropped back to 6,000. Abdominal distention became very marked and the patient expired, apparently of cardiac failure. This patient had suffered from chronic malnutrition for several months prior to his pneumonia from a large esophageal diverticulum.

An ideal result is shown in the following case history:

Case 3: This forty-eight year old man was admitted to the hospital one week after the onset of a cold with some chilly sensations. Physical examination at the time of admission showed only a slight pleural rub in the left chest anteriorly but roentgenogram of the chest showed an extensive infiltration in the left upper lobe, apparently a lobar pneumonia of the upper left lung. The blood culture was sterile. The white blood cell count was 8,800; urine on admission showed heavy albuminuria with a moderate number of hyaline casts and a few white blood cells. The icteric index was 20. On sulfapyridine therapy the temperature decreased from the admission temperature of 103° F. to normal in thirty-six hours, and remained constantly below normal from then on. Physical signs in the chest remained minimal at all times but it was five days after his admission before the X-ray showed evidences of resolution of the pneumonic process.

An example of relapse of the infection following too early discontinuation of the drug and of probable drug fever on too prolonged administration during the second course is seen in the following case history:

Case 4: This was a seventy-eight year old man who had experienced a previous attack of lobar pneumonia of the right lower lobe in April, 1939, which had been treated with sulfapyridine with an excellent response. He was admitted to the hospital on December 27, 1939, with evidence of pneumonia of the right lower lobe. Temperature on admission was 100.5° F., white blood cell count was 13,700 and the pulse rate was 96. On sulfapyridine therapy the temperature dropped to normal within a period of twelve hours and remained there. After four days of perfectly normal temperature, the patient pleaded to be allowed to go home by ambulance and therapy was discontinued. Three days later he was readmitted with evidence of a recurrence of his infection, temperature 101.3° F., pulse 96. Sulfapyridine therapy was again started and within thirty-six hours the temperature reached the normal line. Shortly thereafterwards it increased and continued at an average of approximately 100 to 100.5° F. On the sixth hospital day the sulfapyridine was discontinued and, although the temperature reached 102.5 the following day, it subsequently declined and reached normal thirty-six hours later. The white blood cell count which had been 21,000 on the

second admission had meanwhile declined and at the height of the hyperpyrexia was only 13,000.

Summary

In accordance with the general conception, it is our opinion that the introduction of this specific chemotherapy has vastly increased our therapeutic armamentarium against both lobar and bronchopneumonias. In streptococcal bronchopneumonia and especially a lobar pneumonia sulfapyridine has given dramatic results. Although in this small series of lobar pneumonias treated with sulfapyridine the mortality rate of 16 per cent is more than in many reported series, careful analysis of the fatal cases indicates the presence of extrapulmonary factors which were the main cause of failure.

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