SULPHAMERAZINE TREATMENT OF PNEUMONIA IN ADULTS

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Pneumonia lost many of its terrors with the discovery and development of the sulphonamides, and the results of treatment of this disease are progressively improving. There is, however, a tendency to regard the sulphonamide drugs as superseded by penicillin not only in the severely ill but even in mild conditions where the former have proved adequate. Needles are never pleasant to the patient or convenient to the attendant. We hope to show that sulphonamide treatment for primary pneumonia in adults is satisfactory in the vast majority of cases, and should be given before confirmation of a clinical diagnosis, in the form of bacteriological and radiological reports, is available. Further, we feel that all but the most severe cases in aged or debilitated patients are reduced by this treatment to a two-day fever which can be adequately treated at home. Hospital care, with facilities for fuller investigation and treatment, is needed only for patients who fail to respond rapidly to sulphonamides or who are critically ill or whose condition is otherwise complicated.

Pneumonia commonly occurs without the classical physical signs. We maintain that, in the absence of an influenzal epidemic, patients complaining of respiratory symptoms are suffering from some measure of lung consolidation if they have a temperature higher than 100° F. (37.8° C.) for more than one day. We have encountered many such patients in whom skiagrams have shown segmental or central consolidation, and we consider that all these cases should be given the benefit of a full course of a suitable sulphonamide without delay.

It is very desirable to obtain at the outset, and before treatment is started, a specimen of sputum for complete bacteriological investigation. This will give a reliable indication of the causal organism in 70% of cases. Radiological confirmation that resolution is complete, particularly in every patient over 40, is essential. Patients with carcinoma of the bronchus not infrequently present with pneumonia, but complete clearing rarely occurs.

Sulphamerazine

We do not attempt to prove that any sulphonamide is more successful than penicillin in the treatment of pneumonia (although we have reached this conclusion from a small series of cases that are not statistically significant). Sulphonamide therapy is certainly less troublesome, and with the newer preparations there is no need for frequent dosage, with consequent loss of sleep. Toxic effects are minimal. In this hospital patients may be admitted to any medical ward under the care of any of the physicians, so that treatment is that considered best by the physician concerned and is in no way standardized. By common consent, however, the treatment now used almost invariably is that with sulphamerazine.

Workers in America have compared the pharmacological properties of sulphamerazine with those of other sulphonamides (Hageman *et al.*, 1943; Schmidt *et al.*, 1944b), while its toxic effects have been compared with those of sulphadiazine by Dowling *et al.* (1944) and with those of sulphamezathine by Schmidt, Hughes, *et al.* (1944a). Reviews and clinical evaluations of the use of sulphamerazine in pneu-

monia have been published by Genecin and Nelson (1945), Heffner (1945), and Volini *et al.* (1945).

Sulphamerazine, a methyl homologue of sulphadiazine, is absorbed more rapidly and excreted more slowly than sulphadiazine. At equal blood levels it is no more toxic than sulphadiazine and is far less so than many of the older preparations. As a result, a single dose of sulphamerazine will produce a higher blood level of the drug, and more quickly, than the same dose of sulphadiazine, and this blood level will be longer maintained (Flippin, Reinold, and Geffer, 1943; *Medical Uses of Sulphonamides*, H.M.S.O., 1945; *Lancet*, 1943). Being more soluble than sulphadiazine it presents less risk of urinary obstruction with crystals (Anderson, Oliver, and Keefer, 1944). The rapid absorption renders parenteral administration almost unnecessary, since an oral dose will produce therapeutic blood levels in two hours, while within four hours the blood levels remain the same as those obtained by equal intravenous dosage (Murphy, Clark, and Flippin, 1943). Thus in comparison with older sulphonamides smaller doses of sulphamerazine less frequently given will produce and maintain an adequate blood level (12–15 mg. per 100 ml. of blood). The course we have found satisfactory consists of an initial "loading" dose of 3 g., followed in eight hours by 2 g. and then 1 g. eight-hourly. The doses can be arranged so that patient and attendant can have an uninterrupted night. With this regime a blood level of 15 mg. is reached within four hours (Welch, Mattis, Latven, Benson, and Shiels, 1943). We have found that this level is well maintained throughout treatment. Adequate urinary output must be maintained by giving six pints (3.4 litres) of fluid daily, but alkali is not required, since it decreases tubular reabsorption of the drug and therefore increases its loss by excretion.

In our experience the above dosage is always well tolerated and rapid subjective improvement occurs. The temperature falls to normal in 24 to 36 hours in most cases and never rises more than 1° F. above normal afterwards. Treatment is continued, according to the severity of the case, for 48 to 72 hours after the temperature has reached normal, so that a moderately severe case will need about five days' treatment (18 g. in all). We found no evidence that such a dosage produced a reduction in granulocytes in the blood that could be attributed to the drug. This agrees with the findings of others, using somewhat larger doses (Flippin, Geffer, Domm, and Clark, 1943). Most patients are fit to get up after a week and leave hospital between the tenth and the fourteenth day from admission. Breathing exercises from the day after the temperature has fallen accelerate the disappearance of added sounds in the lungs. Fig. 1 graphically represents the progress of a typical case.

In addition to specific drug therapy we find that adequate sleep on the first night of treatment is best obtained with an injection of 1/4 gr. (16 mg.) of morphine, which also suppresses the painful cough; in older subjects pethidine, 100 mg. by injection, is adequate and in many ways preferable. A linctus for the first two or three days may be helpful to control the cough; a really effective preparation, such as linctus heroin, should be used. Alternatively, 1/12 gr. (5.4 mg.) or 1/6 gr. (11 mg.) of "dicodid," by mouth, is satisfactory. Pleural pain rarely persists long after the start of sulphamerazine, and is well relieved by spraying the chest wall with ethyl chloride; the relief lasts about three hours, and the spray may then be repeated if necessary. We have never resorted to strapping the chest.

Although the illness is shorter and less severe as a result of treatment, full convalescence is essential, since pneumonia affects predominantly those subject to the stresses

of overwork and the risks of overcrowding, and rarely strikes the healthy adult. The patient should be advised to see that his future life is modified so as to avoid a recurrence of those circumstances that rendered him an easier victim to pneumonia. This may mean that a housewife must be advised not to add to her burden by long hours in a factory and the enthusiastic gardener warned against over-indulgence in his hobby.

We have found that a small spike of temperature, up to but rarely exceeding 99.4° F. (37.4° C.), occurs in many cases. This spike was seen in 60% of our successfully treated cases, being found more often where a four-hourly temperature chart was maintained than where the temperature was taken twice daily. The spike occurred most frequently about thirty-six hours after the temperature had settled, and some cases showed two or more such spikes. In no instance was this phenomenon correlated with any

FIG. 1.—Chart of a typical case of severe lobar pneumonia treated with sulphamerazine.

failure of treatment or the development of any complication. It is met with as often in patients under penicillin as under sulphonamide therapy, and we have come to the conclusion that it need cause no misgiving.

Present Series

For this investigation the last 189 proved cases of pneumonia were studied—that is, those occurring since sulphamerazine became easily available. Criteria of diagnosis are clinical signs, supported by radiological evidence of well-defined consolidation, together with (in most cases) the presence of leucocytosis and the isolation of a causal micro-organism. Cases in which the pneumonia occurred as a terminal event in another mortal illness are excluded. In the series there were 101 males and 88 females. The average age for males was 43.0 years and for females 40.5 years, the extremes of age being 13 and 76 years.

Of these 189, 113 were treated with sulphamerazine from the start without a single death; 36 were treated with sulphamezathine (sulphadimethylpyrimidine), with three deaths; and 22 with penicillin, with one death. Combined

treatment was given to 12 patients, one of whom died. The remaining cases were so mild that no specific therapy was deemed necessary. The details of those dying in these series are:

Treated with Sulphamezathine Alone (36 cases, 3 deaths)

1. Man aged 52.—Chronic bronchitis for seven years. History indefinite. Died within two hours of admission. Diagnosis at necropsy: left lower-lobe pneumonia.
2. Man aged 65.—An alcoholic polycythaemic patient. Indefinite chest illness for one month. Severe symptoms for three days. Died within 24 hours of admission. Diagnosis at necropsy: right mid-lobe pneumonia.
3. Woman aged 66.—A known case of aortic stenosis. Fluid complicating right lower-lobe pneumonia. Collapsed three days before admission after nursing dying husband. Severely ill. No response to treatment. Diagnosis confirmed at necropsy.

Treated with Penicillin Alone (22 cases, 1 death)

4. Man aged 59.—Admitted with acute pulmonary oedema. Died within 12 hours of admission. Diagnosis at necropsy: rheumatic aortic stenosis, acute pulmonary oedema, left-sided pneumonia.

Treated with Combined Therapy (12 cases, 1 death)

5. Girl aged 15.—Died 12 hours after admission. Left lower-lobe pneumonia complicating rheumatic mitral stenosis and aortic regurgitation, associated with acute pulmonary oedema. Confirmed at post-mortem examination.

It will be seen that no therapy could offer much, if any, chance of recovery.

The Sulphamerazine Group

The sulphamerazine cases are considered in further detail. Three of the 113 were given sulphamerazine together with penicillin from the outset; one was critically ill, another less severely ill but rather old (66), and the third a case of moderate severity in a soldier, who would probably have responded well to either treatment alone. Among the remaining 110 patients the condition was classified as mild, moderate, or severe, according to the clinical impression. The age distribution, in decades, of these 110 patients is recorded in the following table.

Age Period	No. of Cases	Age Period	No. of Cases
13-20 ..	11	51-60 ..	17
21-30 ..	22	61-70 ..	11
31-40 ..	25	Over 70 ..	3
41-50 ..	21		

Bacteriology

The sputa of 87 cases, in all groups of severity, were examined on admission, and 60 of these yielded on culture a causal micro-organism. The examination thus gave a positive finding in 70%. The pneumococcus was cultured in 53 cases, a haemolytic streptococcus in 10 cases (seven times we encountered both organisms); Friedländer's bacillus in 1 case, and *Staph. aureus* in 3 cases. Of the 27 cases which grew no pathogenic organisms the majority responded to treatment as if they had been pneumococcal in aetiology. Most cultures grew non-pathogenic organisms in addition, most frequently *Neisseria catarrhalis* and *Str. viridans*—the latter rarely in free or pure growth. This finding emphasizes the fact that to be of most value this examination must be carried out on a specimen of real sputum from the lung and not saliva. In young and non-smoking subjects a specimen may be unobtainable.

Results

There were 17 mild cases in the series—9 men (average age 38) and 8 women (average age 37); thus these patients were, on the whole, young. Treatment of all but one was totally successful, fever disappearing in an average of 1.4 days and the patients leaving hospital in 11 days. The average dosage of sulphamerazine was 16.5 g. and the success rate 94%.

The moderately ill patients numbered 59 (31 men and 28 women), the average ages being 40 and 43 respectively. In 50 cases the results were totally successful, the temperature reaching normal in two days and discharge occurring in 15 days on the average. The dosage of drug used was 19 g. and the success rate 85%.

Of the 34 patients classified as severe cases the average age was 42 for both sexes, there being 21 men and 13 women. Sulphamerazine produced a successful response in 27, with the pyrexia settling in 2.2 days and discharge being given in 16 days after an average dosage of 19 g. The success rate here is 79%.

Thus, of 110 patients treated with sulphamerazine when a clinical diagnosis was made 93 gave a response regarded therapeutically as successful—an overall success rate of 84.5%. All cases were followed up in the out-patient department after convalescence if clearing was not demonstrated radiologically before discharge.

Among the successful cases there were 10 which developed small amounts of sterile pleural effusion, and 3 which had relapses of fever responding to a further course of sulphamerazine. Other minor complications were one temporary lobar collapse, one femoral thrombosis, and one abortion. In no case was convalescence seriously delayed.

Cases Given Additional Treatment

In 17 cases the response was deemed inadequate and further treatment was given. Fluid developed in 5 cases in amounts sufficient to justify aspiration. The fluid remained sterile throughout and no empyema occurred in the series. Parenteral penicillin was given to each.

Two cases developed lobar collapse, for which penicillin was administered to prevent a new infection becoming established in the collapse area. One severely ill woman developed a confusional psychosis after 7 g. of the drug, which was stopped and penicillin substituted. Her confusion cleared rapidly and she left hospital on the fifteenth day, her progress delayed neither by her psychosis nor by a small sterile effusion which developed. One moderately ill man with a pneumococcal infection developed a drug fever. After a tendency to early settling his temperature rose again and remained high throughout a course of 20 g. of sulphamerazine, falling critically thereafter, having almost reached normal before a three-day course of penicillin was started—probably unnecessarily.

Six patients seemed refractory to sulphonamides. Three yielded a growth of pneumococci on sputum culture, though the growth was not free, and—unfortunately in the light of events—the drug resistance of these strains was not tested *in vitro*. One case was mild and the temperature subsided by very slow lysis over four weeks, apparently unaffected by sulphamerazine (18 g.) or penicillin (three-hourly for 14 days). The other two (one moderate, one severe) responded promptly to penicillin after sulphamerazine had failed. Two other cases produced no pathogenic organisms from the sputum, and both were severely ill. One responded slowly and became afebrile on the eighth day of treatment, which consisted of sulphamerazine 20 g., producing a short-lived response, together with penicillin from the third to the tenth day. The other gradually improved over nine weeks regardless of treatment, his progress being punctuated by thrombophlebitis at three weeks and a lung abscess in the affected lobe at six weeks. These complications cleared completely by four months from the onset of his illness. The sixth case had 40 g. of sulphapyridine during 28 days before admission, and 18 g. of sulphamerazine resulted in no improvement, but the condition yielded dramatically to penicillin.

Staphylococcal Pneumonia

The remaining two cases were due to *Staph. aureus*. Certain strains of staphylococci are moderately sensitive to sulphamerazine. There were three cases of staphylococcal pneumonia in this series; one case, that of a man of 70, was among those successfully treated. His fever had already subsided when the laboratory reported a pure growth of *Staph. aureus* from his sputum; no relapse occurred after treatment. In the other two progress was not so smooth. The first became afebrile in 36 hours, so treatment was not changed on the bacteriological findings; a relapse followed the end of treatment, and this was promptly and finally dealt with by penicillin (60,000 units three-hourly for seven days). The second case seems typical of this condition, and is described in more detail; the temperature, pulse, and respirations are reproduced in Fig. 2.

A man, aged 34, who had been overworking, was seized at 3.30 p.m. on June 3, 1946, with severe left chest pain, breathing becoming difficult. He sweated profusely, vomited twice, and

FIG. 2.—Chart of a typical case of staphylococcal pneumonia treated with sulphamerazine and penicillin.

felt weak. He had a cough with scanty sputum. Examination showed signs of left basal consolidation when he was admitted the following afternoon. Sulphamerazine was administered in the usual dosage, and produced a reduction in pyrexia to 100° F. (37.8° C.) from the original 103.6° F. (39.8° C.). On the 7th the pneumonic process had extended to the left upper zone, and herpes labialis was present. When on June 9 the bacteriologist reported that staphylococci were present in the sputum penicillin was started. In 30 hours the temperature had dropped to normal, and progress thereafter was uneventful. (The picture in this case was confused by an early finding of pneumococci in the sputum; had this not occurred the case would have been recognized as staphylococcal-resistant to sulphonamide sooner than on the fifth day of treatment.)

Toxic Effects

One patient showed on the third day a transient rubelliform rash which faded in spite of further administration of sulphamerazine. In this case, unlike those described

by Hall and Spink (1943), there was no relapse of temperature with the eruption.

Two women became confused during treatment. One has already been mentioned; she had had only 7 g. and her treatment was changed to penicillin. The other developed a psychotic state only after an adequate course of treatment had been given; the confusion cleared in four days and the pneumonia resolved rapidly. Drug psychosis has been reported by Flippin, Geftter, Domm, and Clark (1943), but both these cases had small doses of sulphonamide, and their condition may have been due to pneumonia rather than its treatment.

Drug fever occurs with all sulphonamides. Geftter *et al.* (1943) reported it in severe cases, most of which had over 40 g. of sulphamerazine. Two cases occurred in this series, the pneumonia responding according to expectation but fever persisting unexplained until a critical fall after stopping the drug incriminated the sulphonamide.

We have encountered no serious toxic manifestations in the use of this sulphonamide, and feel that they should be excessively rare provided that administration is not too prolonged.

Summary

A series of cases of primary pneumonia in adults is presented. No deaths occurred among 113 cases treated with sulphamerazine. Five deaths (7% mortality) occurred among 76 treated with other agents, including combined therapies. The total mortality was 3%.

It is claimed that sulphamerazine, which can be given in relatively small doses at eight-hourly intervals, is a satisfactory therapeutic agent for this disease. The results are such that pneumonia can be treated at home and be reduced to a "two-day fever." Should no response follow within 48 hours the case should be reviewed at once and the facilities provided by the hospital for further investigation and treatment be employed.

The need for radiological demonstration of complete resolution is emphasized, as is the need for adequate convalescence.

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Dr. Samuel Standard, the Associate Professor of Clinical Surgery at New York University, "has found that powder-puffs are a menace to health," reports B.U.P. "Anyone who has seen a powder-puff pulled out of a lady's handbag containing loose change, tobacco dust, and handkerchiefs, clean or otherwise, must have looked in awe as the perspired face and forehead were punished by swift, firm, hasty strokes smeared on fiercely by a deft, practised hand. Twenty-four hours later the owner of the face is surprised to find a crop of pimples spread over the cheek and forehead. In despair, she covers these again and again by the same method, and her wonder grows that her pimples multiply."

ORAL PENICILLIN IN TREATMENT OF PNEUMONIA IN THE ADULT

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A comparative study (Anderson and Ferguson, 1945) of the efficacy of the sulphonamides and penicillin in the treatment of pneumonia showed that there was little to choose between the two methods. Although certain advantages could be claimed for penicillin on account of its lack of toxicity, its use had one great drawback, especially for the general practitioner—the need for repeated intramuscular injections. Early studies with regard to the route of administration of penicillin had suggested that the material was likely to have little effect when given by mouth because of its inactivation by the acid of the gastric juice (Abraham *et al.*, 1941) or because of penicillinase production by coliform organisms (Chain and Florey, 1944). This led different workers to try to combine penicillin with suitable antacids and buffers designed to counteract the stomach acids (e.g., Little and Lumb, 1945). Bunn and his co-workers (1945) used penicillin orally in the treatment of 45 cases of pneumonia and had only one fatality. The material was given in a gelatin capsule; in about half of the cases the capsule contained an oily suspension and in the remainder the ordinary powdered sodium salt was enclosed. However, Finland, Meads, and Ory (1945) came to the conclusion that elaborate buffering devices were unnecessary and that administration with saline or even water was equally valuable in procuring effective therapeutic blood levels. These authors obtained satisfactory results with oral penicillin in the treatment of seven cases of adult pneumonia. Bushby and Harkness (1946), who reviewed the conflicting reports on different methods of administration, used penicillin orally for the treatment of gonorrhoea and were satisfied with the results, which indeed were as good as those obtained with intramuscular penicillin. (It is important to realize that these results were obtained in adults, for Buchanan (1946) has since shown that oral penicillin can be used with excellent effect in infants whose normal achlorhydria was assumed to prevent inactivation of the antibiotic.)

In view of the great variations in the sensitivity of different organisms to the action of penicillin and because of the differences in severity between cases of the same infection, it was felt that there was a need to investigate the efficacy of penicillin administered orally to an unselected series of patients with pneumonia. In this infection, unlike gonorrhoea, the treatment must be capable of dealing with the bacteria not only in the tissues but also in the blood stream; it seemed possible that penicillin given by mouth might be unable to attain concentrations in the blood high enough to quell a bacteraemia.

Material and Methods

The patients comprised in the study were all adult males admitted to the wards of Knightswood Hospital during the winter of 1946–7 in whom the diagnosis of pneumonia was confirmed. They were divided into two groups, one group being given penicillin orally and the other penicillin intramuscularly as a control. There was no conscious selection of patients for either method; on admission they were allocated alternately to the two groups.

Intramuscular Penicillin.—The patients in this group were given an initial dose of 50,000 units, after which successive doses of 20,000 units were administered at four-hourly