SOME PROBLEMS IN THE CHEMOTHERAPY OF PNEUMONIA.


South African Medical Corps.

The newer chemotherapy has marked an important milestone in the history of medicine, no less important than those derived from the work of Pasteur and Lister. In their scope of application the new drugs far exceed the value of such an irreplaceable chemotherapeutic as neoarsphenamine. It now becomes almost inconceivable how we countered bacterial infections before the introduction of the sulphonamides and it is equally difficult to appreciate how we could possibly practise the art of medicine without these drugs to-day. It has been said that the discovery of the sulphonamides will save more lives than wars can destroy. One time dangerous diseases with high mortality rates have now lost their terror both for patient and doctor alike and amongst the more important of these—pneumonia—at one time honoured with the term "captain of death" has been reduced to a very much less formidable enemy of man. The sulphonamides have completely revolutionized our ideas on the treatment of pneumonia and no differences of opinion exist to-day as to the treatment in this disease, which is probably the best evidence available for the value of the drug.

Prior to M & B 693 being placed on the market I was privileged to take part in a clinical experiment, half the number of patients being treated with this new drug whilst the other half acted as controls. The early recovery of the treated cases as compared with the less fortunate controls was at that time a revelation but is to-day just taken for granted as the
normal course of events. The experimental stages are now past history and no question exists as to the specific action of M & B 693 in pneumonia.

The mere introduction of M & B 693 has removed the biggest problem of this disease—the high mortality rate. Problems in the application of the drug still exist; these have become more evident as our experience in the treatment of pneumonia has grown. I propose to discuss some of these features. The following are some of the problems in the chemotherapy of pneumonia which I propose to discuss.

1. Economy in the use of M & B 693 in pneumonia.
2. Treatment of influenzal and broncho-pneumonia.
3. The place of other sulphonamides in the treatment of pneumonia.
4. Toxic effects of the drug and complication of the disease.
5. Prolonged pyrexia.

ECONOMY IN THE USE OF M & B IN PNEUMONIA.

The approach to this problem has been prompted by the available supplies of the drug at present and the likelihood of further economies having to be effected. Its free use has already been restricted in gonococcal infections, the dosage for meningitis must be liberal, and the question of possible economy in the treatment of large numbers of cases of pneumonia has been considered. This problem is closely linked with the precise action of the sulphonamides. Attempts at obtaining a solution to the problem have been made by in vitro and in vivo experiments. At present the answer appears to be that the sulphonamides interfere with the metabolism of the bacteria by either neutralizing the effect of the enzyme or by destroying the metabolite on which the organism feeds. In in vitro experiments it would appear that organisms die out slowly when in contact with a sulphonamide, sterilization taking about twenty-four hours to be complete. Fleming has however shown that in the presence of leucocytes organisms will be killed rapidly when in contact with the drug. These latter conditions would appear to resemble more closely the biochemical changes occurring in man. If the drug produced a rapid bacteriostatic effect, it would be reasonable to suggest that the return of the temperature to normal coincided with the death of the organisms and hence the drug could be discontinued when the temperature reached normal. Under these circumstances, early withdrawal of the drug after the temperature reaches normal should be a fairly safe procedure. If this view is correct, it should result in a considerable saving of the drug, since a quantity approaching that used in the pyrexial period is not infrequently used in the apyrexial stage. More than a year ago I had the opportunity of putting this view to the test and in a small group of cases of African patients it was noted that the results were encouraging in that relapses in these cases were few (Agranat). Another feature which struck me at that time was that the average African patient appeared to be even
more responsive to M & B 693 than the average European; an acutely ill
African patient appeared to respond rapidly to the drug, the temperature
frequently reaching normal within twenty-four hours. During recent months
I have once more had occasion to treat African patients and I have again
tried out the curtailed form of treatment.

On my suggestion a number of cases in hospital were placed on the
"short course treatment" which consisted of avoiding high initial or loading
doses and of discontinuing treatment as soon as the temperature returned
to normal. The remaining cases during the same period under review had
the usual prolonged course of treatment and these acted as a control group
in this experiment.

The records of 185 patients seen over a period of two months were
reviewed, 89 cases being given the "short course treatment" (Group A)
while 63 had the "long course treatment" (Group B) and acted as the
control group. The remaining cases not included in these two groups were
14 cases of bronchopneumonia treated first with sulphanilamide and 5 cases
of pyrexia of more than seven days' duration. Fourteen deaths were also
excluded from this review because 5 cases had on the whole very prolonged
courses of treatment and 8 cases on the average had very little treatment,
dying soon after admission.

<table>
<thead>
<tr>
<th></th>
<th>M &amp; B 693</th>
<th>Relapses</th>
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<tr>
<td>Number of cases</td>
<td>89</td>
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<tr>
<td>Average No. per cent.</td>
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<tr>
<td>Average pyrexial period</td>
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<tr>
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<td>Average dose after fall</td>
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<tr>
<td>of temperature in days</td>
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<tr>
<td>Additional dose after</td>
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<td></td>
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<tr>
<td>period temperature No.</td>
<td>4 grm.</td>
<td></td>
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<tr>
<td>Temperature</td>
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<td>continued</td>
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<tr>
<td>M &amp; B 693</td>
<td>13 grm.</td>
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<tr>
<td>relapse</td>
<td>4 grm.</td>
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<tr>
<td>Average period of relapse</td>
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<tr>
<td>Normal</td>
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The object of this investigation was to compare the results of the short
course and long course treatments. The detailed calculations are omitted
for the sake of brevity and the results are shown in the accompanying table.
The temperature in Group A (short course) and in Group B (long course)
fell to normal in twenty-four hours in 56 and 78 per cent. respectively,
the average pyrexial period being 1·5 and 1·3 days respectively. No further
treatment was administered in Group A after the fall of temperature whereas,
in Group B, the cases were treated for an extra average period of 1·5 days
on the basis of 6 grams of M & B 693 per twenty-four hours. The average
dose in Group A was 9 grams, as compared with 16 grams in Group B. The
relapse rate was 17 per cent in Group A and 19 per cent in Group B.
Some Problems in the Chemotherapy of Pneumonia

average relapse period in both Groups was 1.5 days and the corresponding average doses were 13 grams M & B 693 for Group A and 12 grams for Group B. The short average period of relapse—1.5 days—responded rapidly to the second course of M & B in both Groups alike. A point of interest is that a relapse may occur in the presence of full doses of the drug which is therefore no guarantee against such a relapse. The larger figures in the table have been calculated to the nearest whole number and the smaller ones to the nearest decimal figure. Another point is that a rise of temperature below 100° is not considered as a relapse or recrudescence as such a peak is quite common after the temperature has settled and invariably remains down without further sulphanamide treatment. The relapse usually responds fairly rapidly to a second course of treatment.

It may be said that timid use of the drug is as much a mistake as its use in excess. The above investigation would indicate that in the average African suffering from pneumonia the short course treatment should suffice and a considerable economy of the drug could thus be effected. In the case of a patient whose powers of resistance appear to be depleted treatment may be continued for a day or longer whilst the patient is apyrexial but the above figures do not indicate that there is any special benefit in this procedure.

These remarks refer only to African patients who as I have already remarked appear to be even more responsive to the effects of M & B 693 than the European. Similar procedure of treatment in the European could only be advised after further evidence is available; in most of my European cases during the past twelve months I have advised discontinuing M & B 693 after twenty-four to thirty-six hours apyrexial treatment.

Influenzal and Broncho-Pneumonia.

From a chemotherapeutic aspect the only satisfactory classification of pneumonias is on a bacteriological basis. Anatomical classification has no place in modern therapeutics though it may be of value in the clinical description of the pneumonia and to the pathologist. Influenzal pneumonia is a wide term and may mean anything from a voluminous and deeply congested lung to a lobular or lobar consolidation. True influenzal pneumonia is caused by the virus of influenza. These cases are extremely fatal and usually unresponsive to M & B 693. In most cases, however, influenzal pneumonia is due to the secondary invaders, the pneumococcus, the streptococcus or a mixed flora with Pfeiffer's bacillus, the non-haemolytic streptococcus and the Micrococcus catarrhalis. It is impossible on clinical examination to know which of the organisms are concerned with a pneumonia complicating influenza. Elaborate bacteriological investigations take time and such facilities are not always available. It appears to be a common belief among a number of clinicians that the offending organism in influenzal or broncho-pneumonia will respond to sulphanilamide. This may be true for a certain number of cases but certainly does not refer to most cases. It is incorrect to assume
that a particular organism is responsible for a particular type of pneumonia classified on an anatomical basis. Sulphanilamide may be of value in a case due to the haemolytic streptococcus but to await the result of a bacteriological investigation means the loss of valuable time. Douthwaite recommends that sulphanilamide be used for twenty-four hours and, if no improvement occurs, he advises changing to M & B 693. I cannot see any advantage in this procedure. In this series of 185 cases 8 out of the 14 diagnosed as bronchopneumonia were unsuccessfully treated with sulphanilamide for periods varying from two to six days before being changed over to M & B 693; 7 out of these 8 cases then responded to the latter drug. The same remarks apply to the bacteriology of bronchopneumonia. In view, therefore, of the uncertainty of the bacteriology in cases of influenzal or bronchopneumonia it is advisable to use only M & B 693 in all these cases and avoid the use of sulphanilamide.

**The Place of Other Sulphonamides in Treatment.**

I have had very little experience of the newer drug sulphathiazole, better known as M & B 760, and none with sulphadiazine, a more recently introduced preparation. From reports however it would appear to be that sulphathiazole is less nauseating and much less likely to produce vomiting than M & B 693 though equally effective. Owing to the rapid excretion high loading doses are advised. Sulphadiazine has similar advantages, and in addition its toxic effects are said to be very mild (Billings and Wood). The relative value of these preparations can be gauged from a recent publication (Stahle) of an analysis of 15,000 cases of pneumonia. The mortality rate in 9,195 cases treated with M & B 693 was 8·1 per cent., in 3,666 treated with sulphathiazole the rate was 8·2 per cent. and in 52 cases treated with sulphadiazine the mortality rate was 11·5 per cent. The author concludes that all cases of pneumonia should be treated with sulphathiazole.

Under the present conditions supplies of these newer sulphonamides would not be readily available nor do they appear to have any advantage over M & B 693 in the African. The African patient is on the whole very tolerant to M & B and in the occasional case in which vomiting is troublesome the tablets may be replaced by injections.

**Toxic Effects of the Drug and Complications of the Disease.**

**Toxic Effects.**—The only serious problem arising from the possible toxic effects of the drug is in those cases showing toxic psychosis. In this series six such cases were encountered of whom two died. It is difficult to assess how much of this toxic state is due to the infection and how much to the drug. In general terms the drug should be discontinued as soon as the temperature reaches normal or, if adequate dosage has been maintained, for about five days without the temperature returning to normal. The only other
toxic effect of the drug in this series was in a case of haemolytic anaemia in which the haemoglobin fell from what appeared to be a normal level on admission to about 50 per cent. in two days. Agranulocytosis need not be feared as it seldom appears under fourteen days and blood counts as a routine are therefore rarely necessary during the treatment of a case of pneumonia. Urinary manifestations are also singularly absent.

Complications.—These too are comparatively rare and are not a major problem. In the series under review there were four cases of toxic jaundice, seven cases of pleural effusion requiring aspiration and four cases of empyema. A toxic jaundice usually indicates a severe infection. At one time jaundice was considered to be a contra-indication to the use of the sulphonamides but it has since been realized that the logical procedure is to eliminate the infection causing the hepatitis and hence M & B 693 should be administered in full doses. The four cases in this series recovered though another such case admitted since then died after a few days’ treatment.

Small sterile effusions are fairly common and usually absorb on their own account. Following aspiration in 7 cases the residual temperature disappeared. The incidence of empyema occurring with M & B 693 is no higher than it was before the drug was introduced. One of the 4 cases of this series in whom aspiration had been done whilst waiting for the pus to thicken died rather suddenly and unexpectedly following a convulsion. Although a post-mortem was not done it was thought that he might have had a metastatic cerebral abscess.

Cases of Prolonged Pyrexia.

These cases form one of the major problems in the chemotherapy of pneumonia. If the infection does not respond to ample dosage of the drug for three days it is my opinion that the sulphonamides will not effect a cure. The drug is however seldom discontinued during the primary pyrexial period however unconvinced one may be of its value after it has been administered without effect for a few days. It is not infrequently stated that the incidence of prolonged pyrexias following the use of M & B 693 is greater than in the days when natural resolution occurred; this is open to doubt. These cases are usually labelled as unresolved pneumonia and treatment with M & B 693 is continued for prolonged periods in many cases; usually with little or no benefit. The proof tendered in support of a diagnosis of unresolved pneumonia is the physical signs of consolidation in the lobe or lobes originally involved. This is in fact no proof for in all cases of pneumonia although the temperature has settled the pathological process in the lung proceeds through the usual stages to resolution. These signs may be present for several weeks and are therefore no evidence that the temperature is due to an unresolved pneumonia, which diagnosis is made too often. Davidson has recently remarked that “a warning is necessary as to the continued abuse of the expression—unresolved pneumonia.” No doubt this condition does exist but before this diagnosis is made the case must be
reviewed on a systematic basis to exclude any other cause for the temperature. Amongst the possible causes to be considered are the following:

Extension of the Pneumonia.—This may occur during the administration of the drug or it may appear in a relapse. In the latter instance it is probably due to a different type of pneumococcus. Extension during treatment is always a puzzling occurrence and makes the action of the drug difficult to understand. Under these circumstances it is necessary to continue giving the drug in full doses even though it has already been administered for two or three days.

Tuberculous Pneumonia.—The sputum in every case of persistent pyrexia should be examined for T.B. No cases of tuberculous pneumonia appeared in this series although one such has occurred since and I have also previously met this as a cause of the continued temperature.

A Pneumococcus Unresponsive to M & B 693.—This too is a comparatively rare finding but occurs more frequently than T.B. Three such cases appeared in this investigation, a natural resolution occurring on about the seventh day. M & B 693 was in one case administered for four days and in two others for six days without making any impression on the temperature. There is always a tendency in these cases to continue with the drug in the hope that the particular case treated may prove an exception. It is most unusual to find a case responding to the drug after three days. The organism which in these cases is unresponsive to the sulphonamide appears to be a particular type or strain of pneumococcus or the non-hæmolytic streptococcus or the mixed flora found in some cases of influenza. The condition is not caused by drug-fastness, which, however, may be induced by small doses over long periods.

Pneumonic Complications.—Amongst the commonest causes for a prolonged pyrexia are pleural effusion, empyema, lung abscess (particularly small multiple lung abscesses), pericarditis, arthritis, meningitis and septicaemic pneumonia. A very common cause for a moderate pyrexia is a small collection of fluid in the pleural cavity. Physical signs may be misleading; an exploration should invariably be performed whenever residual lung signs persist with a temperature. A pericardial rub should be listened for and the joints examined. Headache and pains in the back may be signs of an early pneumococcal meningitis. Two such cases complained of these symptoms for several days before developing neck rigidity. Early lumbar puncture should be done. Bone complications are rare but in one case a pure culture of pneumococcus was obtained from a case of osteo-periostitis of the tibia following a lobar pneumonia. Pneumococcal endocarditis may complicate a septicaemic pneumonia though this is a rare finding.

Persistent Pyrexia Due to Other Diseases Complicating the Pneumonia.

Malaria.—A single peak of temperature of 101° to 104° F. often occurs after the temperature has settled and appears to be due to malaria in most
cases. Often such a temperature in the presence of the residual signs in the chest is incorrectly ascribed to a relapse and the patient is again given M & B 693. Diagnosis of a relapse is only justifiable if the temperature is accompanied by an increased respiratory rate and blood-stained sputum in addition to the signs in the chest.

Amœbiasis.—It would appear to be a coincidence that two or probably three of the four cases of prolonged pyrexia still in hospital have been due to this cause, the temperature having responded to the appropriate treatment. In one case anchovy paste sputum gave a pointer to the diagnosis and in the others the liver was somewhat enlarged and tender. In no case were amœbæ recovered.

Case No. 26892 is an example of pneumonia with amœbiasis. Admitted on March 30, 1942, with rigors, cough and abdominal pains. Rales present at right base. On April 9 temperature rose to 103° F. with consolidation at right base. Six grams M & B 693 prescribed daily for nine days. Temperature remittent. Treatment repeated on April 24 for three days. Total dose 72 grams. On April 26 saw patient coughing up anchovy paste sputum. Emetine produced subsidence of the temperature in three to four days. X-ray showed a funnel shaped shadow on the right diaphragm fanning out into the lung; the appearances were highly suggestive of an abscess from the liver perforating the diaphragm.

Another case had a temperature for nearly two months following his pneumonia. A leucocytosis and remittent temperature ranging from normal in the morning to 104° F. in the evening strongly suggested a pocket of pus somewhere. Repeated explorations and X-rays of the chest excluded this as the source. Liver abscess was suspected but no pus was found by the surgeon. His condition is improved, his temperature has returned to normal and the physical signs at the right bases have disappeared. It is very likely that the condition has been due to an amœbic hepatitis as originally considered.

Intercurrent Infections.—There is no reason why a patient may not be suffering from any other disease which may become manifest after the pneumonia has settled. Appropriate investigations should be undertaken.

Unresolved Pneumonia.—Only after all the above possibilities have been considered and excluded should this diagnosis be made. X-ray will show some loss of translucency. Two such cases have occurred in this series, taking about six weeks to settle. Sulphonamides do not hasten resolution.

On review of the possible causes of a continued pyrexia it becomes apparent that very few of these cases require more M & B 693, extension of the pneumonia and pneumococcal meningitis being exceptions. The ineffectiveness of the sulphonamides in the presence of an effusion or collection of pus should be borne in mind. Considerable economy in the use of M & B 693 could also be effected in a large number of these cases of prolonged pyrexia.

Analysis of the Deaths.

Fourteen deaths occurred during the period under review, giving a mortality rate of 7·5 per cent. These include seven cases who died within
twenty-four hours, some of them practically on admission, before any or more than the first few doses of the drug could be given. Three died from lobar pneumonia, two from bronchopneumonia, eight from influenzal pneumonia and one from an empyema.

3 Cases of Lobar Pneumonia.

Case 1.—Admitted 15.2.42. Consolidation R.L.L. Had 42 g. M & B 693 and 32 g. sulphanilamide. Died 1.3.42. P.M., right lower lobe honeycombed with small abscesses.

Case 2.—Admitted 21.2.42. Consolidation L.L.L., pyrexial for three weeks. Had 92 g. M & B 693. Died 12.3.42. No P.M.

Case 3.—Admitted afebrile on 7.4.42. Bilateral basal pneumonia diagnosed four days later. Had 7 g. M & B 693. Died same day. No P.M.

2 Cases of Bronchopneumonia.

Case 4.—Admitted 19.3.42. Pyrexial five days. Had 34 g. M & B 693. Died 24.3.42. No P.M.

Case 5.—Admitted 18.3.42. Pyrexial nine days. Had 18 g. M & B 693; discontinued owing to toxic psychosis. Died afebrile one week later. P.M., bilateral lobular pneumonia.

8 Cases of Influenzal Pneumonia.

Case 6.—Admitted 3.3.42. Had 6 g. M & B 693. Died twelve hours after admission. P.M., influenzal pneumonia.

Case 7.—Admitted 4.3.42. Had 4 g. M & B 693. Died six hours after admission. No P.M.

Case 8.—Admitted 25.3.42. Had 3 g. sulphanilamide. Died eight hours after admission. P.M., influenzal pneumonia with suprarenal haemorrhage.

Case 9.—Admitted 10.3.42. Died on admission. P.M., influenzal pneumonia.

Case 10.—Admitted 29.3.42. Had 6 g. sulphanilamide. Died eighteen hours after admission. No P.M.

Case 11.—Admitted 18.3.42. Had 24 g. M & B 693. Toxic psychosis. Temperature normal two days before death. No P.M.

Case 12.—Admitted 22.4.42. No M & B. Died fifteen hours later. P.M., influenzal pneumonia with suprarenal haemorrhage.

Case 13.—Admitted 22.4.42. No M & B. Died fifteen hours later. P.M., influenzal pneumonia with suprarenal haemorrhage.

Case of Emphyema.

Case 14.—Admitted 15.4.42. R.L.L. consolidation. Temperature responded to 12 g. M & B 693, with recurrence. Chest explored 27.4.42. Watery pus aspirated. Pus of similar consistence aspirated on 1.5.42. Died following fit on 8.5.42. No P.M., but trend of events suggested death from a metastatic brain abscess.

Deaths occurring within the first few days of pyrexia are due to a peripheral vascular failure produced by toxæmia of the pneumonia. These are the cases in which M & B 693 fails. When pyrexia is prolonged and no other cause can be found to account for this, death is not infrequently due to multiple small abscesses in the lobe involved, as illustrated by Case 1; this type of case is usually diagnosed as "unresolved pneumonia." The prognosis in bronchopneumonia is no different to that of lobar pneumonia excepting where the age of the patient is a factor; in both these types
of pneumonia the prognosis is entirely dependent upon the response of the organism to the drug. Most of the deaths in this series were caused by influenzal pneumonia to which the African is particularly vulnerable. M & B 693 has little if any effect on the virus of influenza. It is interesting to note that the P.M. findings are not infrequently associated with haemorrhage into the suprarenals.

I would say on review of the deaths that it would appear that none of these could have been avoided. The only feature to be noted was the apparent unnecessary prolongation of M & B 693 (70 to 90 grams in several cases).

In conclusion it has become apparent that since the introduction of the sulphonamides problems in treatment have changed from those concerned with a high mortality to those dealing with prolonged pyrexia, complications and such questions as dosage. In connexion with the last named a considerable saving of the drug could be effected as has been indicated. This also applies to the treatment of prolonged pyrexias. Before the diagnosis of unresolved pneumonia is applied very full investigations and repeated examinations must be done to exclude any of the other and more frequent causes of continued pyrexia. The application of the newer drugs is of interest but under present conditions of little practical advantage over M & B 693. I regret that owing to time factors I have been unable to make this review a wider one. Under the circumstances I have tried to present a few problems in connexion with the chemotherapy of pneumonia as particularly reflected in my recent experience with the African patient.

I wish to express my thanks to the D.M.S. and the C.O. of the General Hospital for permission to publish this paper. I am very grateful to Lt.-Col. A. H. Macklin for his advice and help and to the Medical Officers of the Hospital for their full co-operation.

REFERENCES.