The VALUE

of

CHEMOTHERAPY with SULPHONAMIDES

in some

COMMON ZYMOTIC DISEASES

assessed from personal observations.

THESIS

by

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Sulphonamide Chemotherapy was first introduced into therapeutics by Colebrook and Kenny in 1936 working on the problem of the treatment of puerperal infections. Their work was based on the observations of Domagk in 1935. He found that experimental mice were protected against lethal doses of haemolytic streptococci by the administration of prontosil, a compound of sulphanilamide. The power of the sulphanilamide to inhibit the growth of the invading streptococci was shown to be dependent on some way on the living organism. It has been suggested that the drug alters the bacteria in such a way as to favour natural phagocytosis, but the exact mode of action is still uncertain.

Colebrook (1936) treating cases of puerperal infection at Queen Charlotte's Hospital, London, demonstrated that prontosil was capable of producing dramatic improvement and reduction of mortality in patients infected with haemolytic streptococci of the highly virulent type A. It was immediately recognised that this discovery would have considereble significance in the treatment of the numerous diseases due to

streptococcal infection and particularly the commoner ones such as scarlet fever and erysipelas.

Success with streptococcal infections naturally suggested trials of the new drug in other infections.

Whitby (1937) was able to show that sulphanilamide besides being effective against streptococci, was also similarly active against, meningococci, gonococci and bacillus coli.

At the same time other sulphonamides were introduced in an attempt to find a specific remedy for infections with organisms such as staphlococci and pneumococci.

In 1938, Whitby announced a new Sulphonamide, viz. 2 (p:aminobenzenesulphonamido) pyridine, commonly known as M.& B.693. with bacteriostatic powers over pneumococci equal to the action of sulphanilamide over streptococci. Moreover the new drug was just as effective against streptococci, meningococci and gonococci.

Such discoveries naturally stimulated interest in the treatment of the common diseases known to be caused by those organisms and sulphonamides came to be used in Streptococcal infections of all kinds, Gonococcal infections, Meningococcal Meningitis, Pyelitis and Cystitis due to B.coli infection and the Pneumonias. Some of those diseases have a high mortality rate and the frequency with which all of them occur in the practice of medicine, made this innovation in treatment

a matter of first rate importance.

New therapeutic agents must necessarily be used with caution till their dangers and their value are established. The production of those new chemical compounds, however, has been so rapid that it has been difficult to assess their limitations, their contra-indications and their clinical worth by proper extensive trials. The potential danger of this state of affairs is apparent.

Before new treatments supercede the old, they must show an improvement in results and prove themselves to be at least as safe and convenient in application as the old.

This new treatment is of especial interest in the work of an infectious diseases hospital. Moreover in such an hospital it is usually possible to obtain a series of patients, suffering from the commoner infections. sufficiently large to give significant results in the evaluation of methods of treatment.

Since 1935 I have been in charge of Thornton Isolation Hospital - an hospital of about 80 beds serving the populous south-west district of the County of Fife. During the past three years therefore, I have had the opportunity of studying the effects of sulphon-amides on a large number of patients under constant conditions in hospital, besides using the drug in suitable cases occurring in my private practice.

The Sulphonamides which I have used in those investigations are:-

1. Sulphanilamide.

   This in the great majority of cases was as Streptocide (Evans) and in the others, as Prontosil Album (Bayer).

2. Compounds of Sulphanilamide.

   1. Prontosil Red. (Bayer)

   2.a.Proseptasine.)(May & Baker)
   b.Soluseptasine.) Benzyl derivatives of sulphanilamide.

   3. Uleron (Bayer)

3. M.& B.693. or 2(b.aminobenzenesulphonamido) pyridine.

I propose to give an account of the clinical experience gained in the use of those new drugs, and also, a summary of the results obtained from their exhibition in the treatment of streptococcal infections, (particularly Scarlet Fever and Erysipelas),urinary infection with Coliform bacilli, meningococcal meningitis, gonorrhoeal ophthalmia neonatorum, para-typhoid carriers and pneumonia.

Streptococcal Infections.

When Sulphanilamide was shown to act as a specific remedy for puerperal infections with haemolytic streptococci, it was immediately put on trial in the treatment of diseases in which the haemolytic streptococcus was known to be the causal agent. Scarlet fever, which is numerically the predominating disease in most infectious diseases hospitals, and which is always caused by infection with haemolytic streptococci, offered the most promising field for treatment with the new drug. Other diseases due to haemolytic streptococcal infection, not so common as scarlet fever, but none the less important on account of their severity, such as Erysipelas and Streptococcal empyema were reasonably expected to be within the scope of the new treatment.

For the past three years therefore, sulphanilamide or one of its compounds have been used in the treatment of scarlet fever, erysipelas and streptococcal empyema. As will be discussed later, it was also used in the treatment of puerperal infections, many of which were probably due to streptococcal invasion.

1. Scarlet Fever.

It is now generally accepted that Scarlet Fever is always due to an infection of some part of the body -

usually the fauces - with Streptococci,which may conform to any one of the twenty-eight different types of haemolytic streptococcus pathogenic to man. (Banks 1939).

Clinically the severity of individual cases of scarlet fever varies within very wide limits.

In a rural area such as is served by Thornton Isolation Hospital, scarlet fever tends to occur in small local epidemics. Each epidemic produces cases, which are similar in severity, which have the same features in the initial stage of the disease and which tend to develop the same complications. Thus, cases from one village may have the faucial inflammation as the most salient feature, whereas cases from another area may have a profuse rash and mild throat symptoms; in one epidemic, there may be a noticable tendency to otitis media as a complication and in another an increase in the rate of renal complications. Those observed clinical facts corroborate the bacteriological evidence that scarlet fever may be produced by different types of haemolytic streptocccci, if the reasonable assumption is made that each type has different predilections in its attack on the body.

It is therefore impossible to assess the value of any particular treatment, except in a large series of cases. Moreover the only certain method of getting reliable results is by selecting every second patient

for the therapeutic trial and using the others as controls.

In the great majority of cases, Scarlet fever is not a dangerous disease and the mortality rate is low. Complications however are common and cause a good deal of disability and ill health.

The assessment of the value of any treatment therefore cannot be based on the mortality rate but must be made on (a) the relief afforded during the acute stage and on (b) the reduction of the incidence of complications.

About the beginning of 1937, I began to treat Scarlet fever patients with Sulphanilamide. At first the sulphanilamide was used cautiously and patients to be treated with it were selected in a haphazard way. After a few months, when it was seen that the drug could be safely used in all ages without severe toxic symptoms, alternate patients were given the sulphanilamide from the time of admission to hospital. This was continued till July 1939.

Throughout this test period, the preparation of sulphanilamide used was Streptocide (Evans). This was given by mouth in tablets each containing $\frac{1}{4}$ gram or $\frac{1}{2}$ gram of Sulphanilamide.

The daily dose of sulphanilamide varied according to the age of the patient; $\frac{3}{4}$ gm. was given to children

up to five years of age, 1½ gms. were given to school children and 3 gms. to older patients per day. This amount was given in three equal doses. When a patient was admitted in an acutely ill condition the first dose was doubled.

The full daily amount of the sulphanilamide was continued till the temperature became normal - thereafter it was reduced by a third of the daily amount each day for three days.

With recurrence of the fever the sulphanilamide was recommenced and administered as at the onset.

In this manner 224 patients suffering from Scarlet Fever were treated with Sulphanilamide.

For control purposes, I have records of a series of 338 patients suffering from Scarlet Fever treated in hospital over the same period of time and in exactly the same manner apart from the fact that no sulphanilamide was given. The period of time occupied by the control series overlaps that of the test series both before and after.

A few of the severe cases in both groups were given anti-streptococcal serum on admission.

All cases in which the diagnosis was in doubt have been excluded from both series.

The cases under review occurred in several minor epidemics of varying severity and/in one major epidemic

during the winter 1937 to 1938 when the disease met with was more than usually severe, besides those occurring in the usual sporadic form.

Patients suffering from Scarlet Fever are very rarely admitted to hospital before the appearance of the rash has made the diagnosis clear. Hospital treatment therefore is seldom instituted before the second day of illness.

In both the control and the test series I found that 90% of the patients were admitted within the first 72 hours of the onset of the illness. Also, in each series, all but 5% of the patients had an elevated temperature on admission to hospital.

Those factors being constant, the number of days from the onset of the illness till the patient became afebrile is a convenient and moderately reliable standard of comparison of the severity of the initial acute phase of the disease in the two series.

The cases in each series were therefore grouped according to the day of illness on which the temperature returned to normal and remained normal. The percentage number in the group for each day in each series is given in the following table for convenience in comparison.

Day of illness on which temperature became normal.									
1.	2	3	4	5	6	7	8	9	10 & over
Patients treated with Sulphanilamide.									
-	3.6%	11.6%	22.3%	28.5%	16.1%	4.9%	5.8%	2.7%	3.6%
Control Series.									
-	5.3%	19.5%	23.9%	24.8%	11.5%	5.4%	2.9%	2.1%	2.1%

As will be readily seen from the table, there is no evidence that the sulphanilamide hastened the fall of temperature in the acute stage of the disease.

Those figures corroborate the clinical findings during the experiment. It appeared to me then, that the patients treated with sulphanilamide did not improve any more quickly than the untreated cases. The drug had no obvious effect on acutely ill, toxic patients, and the temperature often remained at a high level even after three days treatment. In one instance, a child of 1½ years suffering from malignant scarlet fever, following a burn on the arm, died 24 hours after admission, although she was given both sulphanilamide and anti-scarlatinal serum. This was the only fatal case during the period reviewed and is not included in the series.

The chief danger of scarlet fever is undoubtedly in the risk of complications. Any investigation of the value of methods of treatment must therefore depend largely on an examination of the late results of

treatment and the incidence of the various complications.

A summary of the complications occurring in the patients in each series has been made. Those are grouped in the following categories, and the number in each expressed as a percentage of the number of patients in the series.

1. Ear, Throat & Nose complications.

   This group includes otitis media, discharging ears, rhinitis and persistent septic conditions of tonsils.

2. Cervical Adenitis.

   The cervical glands are practically always swollen and tender during the acute stage. This primary adenitis was disregarded. The patients included in this group all had secondary swellings of the cervical glands, usually in the second or third week of illness, and almost always it was attended by elevation of temperature. In a certain number in each series, the swelling went on to abscess formation, but those cases have not been separated.

3. Nephritis.

   Cases of all grades of severity from albuminuria to haemorrhagic nephritis are grouped together. Cases of transient albuminuria during the initial febrile illness are not included.

4. Heart complications.

   The criterion for inclusion in this group has been tachycardia, irregularity of the heart's action, cardiac murmurs or enlargement sufficient to warrant the patient being kept in bed longer than usual, on this account.

5. Rheumatism.

   This has always been in the form of joint pains with or without swelling, and elevation of temperature,

The results are set forth in the following table:

Type of Complication	Ear, Throat & Nose Complications	Cervical Adenitis	Nephritis	Heart Complications.	Rheumatism.
Series treated with Sulphanilamide	11.5%	12.5%	2.5%	9%	3%
Control Series.	7.5%	11.5%	2%	3.5%	.6%

Examination of the table shows at once that the incidence of complications in the patients treated with Sulphanilamide was actually greater than in the control series.

This again is in accordance with the impression formed in the wards during the test period.

The slightly greater frequency of complications in the patients treated with sulphanilamide might suggest, that the drug had a harmful effect on the course of the disease. The difference is too small, in my opinion, to be conclusive regarding this point, though the question of toxicity of the drug as a possible cause of the increase in complications cannot be disregarded entirely.

Throughout the experiment some of the patients treated with sulphanilamide showed evidence of mild toxic reactions to the drug, but, in no case was there symptoms of a serious nature.

The most frequent toxic sign was cyanosis, noticable as a dusky blue colour of the lips and finger tips. This did not inconvenience the patient in any way and did not appear to be dangerous. It was usually regarded as a caution signal and in one or two instances the drug was stopped more quickly than usual on this account. The cyanosis disappeared in 24 hours or so after the drug was stopped.

Nausea was a fairly common reaction to the drug but vomiting was rare.

A few patients developed urticarial, or macular rashes on the limbs and trunk. Those skin eruptions faded rapidly when the drug was stopped.

Throughout the experiment, patients, while having sulphanilamide were given no saline aperients, and no food or medicine rich in sulphur. This precaution certainly reduces the risk of toxic reactions, particularly the risk of cyanosis.

Young children appear to tolerate the drug rather better than adults.

On the whole, I think the toxic symptoms were not sufficiently serious or of sufficient gravity to cause the increase in the incidence of complications in the patients treated with Sulphanilamide.

The Manufacturers of the drug issued a warning that there might be a risk of the sulphanilamide causing renal damage in some cases. It will be noted from the table

that the difference between the treated and untreated patients as regards renal damage is insignificant, showing that the drug had apparently no deleterious effects on the kidney.

Some of the patients with late complications of scarlet fever, such as otitis media, rhinitis and glandular abscesses were treated with sulphanilamide orally. I have not a sufficiently large number to draw definite conclusions and it is extremely difficult to get any idea of the value of a particular treatment when the disease process is so variable. My impression, however, is that Sulphanilamide is of no value whatever in the cervical adenitis and of doubtful value in otitis media and rhinitis.

In otitis media, [redacted] rhinitis and in septic skin conditions secondary to them, direct application of the sulphanilamide in the form of ointment or drops has been tried with successful results.

2. Erysipelas.

Since 1936 I have treated 54 patients suffering from erysipelas with sulphanilamide and compounds of sulphanilamide. Owing to the lack of material it was not possible to have another series of patients to act as controls.

The disease met with was extremely variable both as regards the site and the extent of the inflammation.

There were no deaths in the series but this is of little significance in a disease which is rarely fatal except in very young or debilitated patients.

The success of any treatment of erysipelas must be judged by the effect on the fever and toxaemia caused by the disease and by the arrest of the spread of the inflammatory process in the skin.

In this small series, which included patients of all ages, those criteria were so varied that a numerical statement of results would be without value.

I shall therefore give only an account of my clinical impressions formed during the course of treatment.

At first Prontosil Red (Bayer) was the preparation used. Adults were given 10 c.c. to 30 c.c. per day, intramuscularly, depending on the severity of the disease. Children were given ½ to ¼ of this amount. Later sulphanilamide as Streptocide (Evans) was given by mouth

in doses of ¾ gm. to 3 gms. per day depending on the age of the patient and the severity of the disease. In some cases, treatment was instituted by an intramuscular injection and then continued by oral administration. Proseptasine and Soluseptasine (both made by May & Baker) were used in some cases in a similar manner.

All of the patients in the series showed an improvement within 24 to 48 hours of the commencement of the treatment with the sulphanilamide preparation. This was evidenced by a fall in temperature, a lessening of the toxaemia and a subsidence of the erysipelatous inflammation.

As far as could be ascertained there was no difference in the results with the different compounds of sulphanilamide and the pure sulphanilamide.

Oral administration was found to be just as effective as intramuscular injection. In some cases the drug given by mouth appeared to give better results than by the intramuscular route.

It was found that it was necessary to continue the treatment for a few days after the patient had become afebrile, in order to avoid recurrence of the disease.

Two instances of the efficacy of this chemotherapy in erysipelas are given for illustration.

Case 1. A child of two months was admitted to hospital on 14/2/37 in her fourth day of illness.

On admission the temperature was 103.6°F, and there was erysipelas involving the right ear, right

cheek, right occipital region and across the nape of the neck.

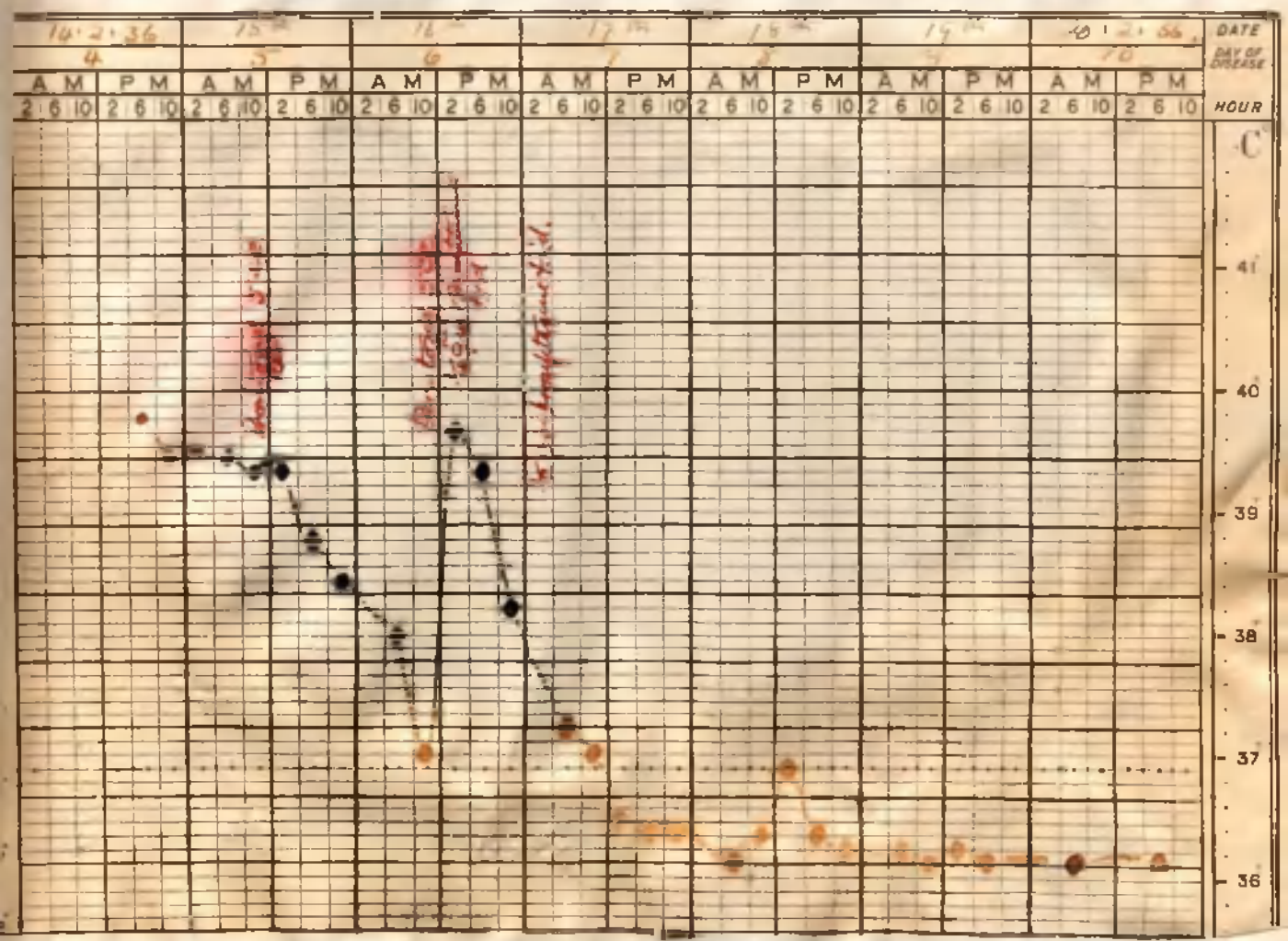
On the 5th day of illness the inflammation had spread across both cheeks and the temperature was 103°F. 5 c.c. Prontosil were given at mid-day and the temperature gradually fell during the ensuing 24 hours.

On the 6th day of illness, the inflammation was still spreading, the general condition was deteriorating and in the afternoon the temperature which had fallen almost to normal, again rose to 103.4°F. A second 5 c.c. of Prontosil was given intramuscularly and $\frac{3}{4}$ gm. of Proseptasine was given by mouth in three doses.

On the morning of the 7th day of illness the temperature had fallen to 99 F and the general condition was improved although during the night there had been further spread of the inflammation involving both arms and both forearms and most of the back. $1\frac{1}{2}$ gms. of Proseptasine was given in three doses throughout the day. The temperature fell to normal.

On the 8th day of illness the inflammation was subsiding and the child was very well otherwise.

On the 13th day the patient was discharged from hospital, well.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A copy of the temperature chart of this case is given.

The only alarming feature of the case was the temporary brignt pink colour of the baby following the injections of Prontosil.

This case is quoted because erysipelas in such a young subject has always been regarded as having a grave prognosis.

Case 11.

In February 1937, a lady aged 70 years of age with chronic nephritis, high blood pressure and failing heart developed a patch of erysipelas on her nose. This was observed at 10 a.m. as a red spot and by 10 p.m. of the same day the whole nose was fiery red and the patient's temperature was elevated. She was immediately given ½ gm. of sulphanilamide by mouth and this was continued ½ gm. three times the following day. Within 24 hours the inflammation was subsided and the sulphanilamide was stopped. The erysipelas with elevated temperature reappeared two days later and again subsided following administration of sulphanilamide. The drug was continued for several days without recurrence of the inflammation.

Although the kidney function was seriously impaired there was no evidence of immediate or late toxic effects of the drug.

The preparation in this instance was Prontosil Album (Bayer).

A noticable feature in this series of cases was that although the ordinary erysipelatous inflammation subsided quickly following sulphanilamide administration, localised pockets of inflammation were not so amenable to this treatment.

The following case illustrates this clinical fact.

An infant, 3 weeks old, was admitted to hospital on 14/3/38 with severe erysipelas over the whole abdomen apparently originating from the umbilicus.

12½ c.c. of Prontosil were given intramuscularly in five doses during the first 24 hours in hospital and 2½ c.c. per day thereafter for the following 3 days.

By 17/3/38 the disease was arrested and all inflammation had subsided excepting an abscess formation in the umbilicus.

On 18/3/38 the Prontosil was stopped but on 22/3/38 the erysipelas had recurred and the temperature was again elevated. The erysipelas had again spread from the umbilicus. Daily doses of 2½ c.c. Prontosil intramuscularly were recommenced and the erysipelas again cleared rapidly leaving only a hard indurated area round the umbilicus. The prontosil was again stopped on 27/3/38, although there was still a hard mass deep to the umbilicus.

On 29/3/38 with a sharp rise of temperature the umbilicus began to discharge pus freely. There was no recurrence of the erysipelas and the whole condition cleared up rapidly.

On 9/4/38 the child was discharged from hospital well with the umbilicus completely healed.

Similar experiences with other cases of erysipelas having abscess formations prior to the administration of sulphanilamide, corroborate the fact that sulphanilamide chemotherapy is effective against the diffuse inflammation of erysipelas only, and is not active in curing an inflammatory process which has become walled off as in the formation of an abscess.

All the patients with erysipelas while being treated with sulphanilamide etc. were having a light diet containing no foods known to be rich in sulphur. Saline and sulphur laxatives were avoided. In no case was there evidence of serious toxic symptoms.

Cyanosis and nausea occurred occasionally but were never sufficient to disturb the patient to any extent or

to require discontinuance of the drug.

5. Streptococcal Empyema.

During 1937 three patients suffering from streptococcal empyema were treated with sulphanilamide preparations; two were treated with sulphanilamide given as Streptocide (Evans) and one with Proseptasine (benzyl sulphanilamide) M.& B.

In two of the cases the empyema developed following influenzal pneumonia and in the other it resulted from a puerperal infection.

Case 1.

A man, 30 years of age, was admitted to hospital in January 1937, suffering from influenzal pneumonia. Ten days later he developed empyema. Aspiration gave a thin purulent fluid containing streptococcus haemolyticus in pure culture. He was given $\frac{3}{4}$ gram of proseptasine per day, and his temperature, pulse and respirations returned to normal. Nevertheless thick pus collected in the pleural cavity and I found it necessary to resect a piece of rib to establish free drainage. He made an uneventful recovery following his operation.

Case 11.

A man, aged 26 years, was admitted to hospital on 26/3/37 with influenzal pneumonia of 10 days duration. On admission he was in extreme distress with dyspnoea and cyanosis. Temperature 103°F. Pulse rate 130 p.min. and respirations 58 p.min.

There were obvious signs of fluid in the right pleural cavity and on aspiration 18 ounces of thin purulent fluid were withdrawn.

Culture of the fluid was reported as giving a pure growth of streptococcus haemolyticus.

$\frac{1}{2}$ gm. of sulphanilamide was given four hourly.

Aspiration of the fluid from the pleural cavity was repeated on 28/3/37 and 2/4/37 - 2 ounces of thin pus being withdrawn on each occasion.

Clinical signs continued to indicate improvement and at the next aspiration on 10/4/37 no fluid could be obtained. His general condition improved gradually and his temperature, pulse rate and respirations were normal from 20/4/37.

Exploration of the chest on 1/5/37 gave no fluid. He was discharged fit on 17/5/37.

His streptococcal empyema was thus cleared with aspiration of pleural fluid on three occasions only and without recourse to surgical drainage.

Case 111.

In June 1937, a woman, aged 30 years was admitted to hospital with puerperal infection. Besides the puerperal parametritis she was found to have fluid in the left pleural cavity. Aspiration gave thin pus which was reported to give a pure streptococcal growth on culture.

She was given ½ gm. of sulphanilamide four hourly. Her chest was aspirated on five occasions and the pus never became thick.

Her chest cleared completely - it was possible to verify the result in this case by X Ray - without any need for rib resection.

Those three cases suggest that sulphanilamide is of value in the treatment of streptococcal empyema and that, if given early enough and in sufficient dosage, it will be possible for the pleural fluid to be cleared by aspiration alone.

The failure of the proseptasine to prevent thick pus formation may have been due to insufficient dosage in the early stage of the empyema or it may have been due to the different composition of the drug. The drug appeared to improve the condition of the patient by lessening toxaemia. Thus he was afebrile while

taking the drug in spite of the collection of thick pus in the pleural cavity.

From this experience it is certainly justifiable to treat cases of Streptococcal empyema with sulphanilamide in large doses while the pleural fluid is being aspirated. Some cases will probably be cured by aspiration without giving the drug, but, I think simultaneous administration of sulphanilamide will tend to make less frequent, the necessity for subsequent operation.

4. Puerperal Infections.

During the past two years 40 patients suffering from puerperal sepsis have been treated in Thornton Isolation Hospital, and Prontosil or Sulphanilamide has been used in every case.

Puerperal sepsis may be caused by infection with any one of several different organisms, though it is recognised that a high percentage of the serious cases are due to infection with haemolytic streptococcus.

Owing to the lack of convenient laboratory facilities at Thornton it has not been possible to make a bacteriological grouping of the patients in the series. For this reason any attempt to analyse the results of treatment would be valueless.

I shall therefore give only a general statement of my clinical findings.

From my experience, I have reason to believe that

sulphanilamide therapy is a valuable aid in treating puerperal infections. In one or two cases who were desperately ill the course of the disease appeared to be dramatically checked by the drug.

The action of the drug was not constant, however, Several patients died or had protracted febrile illnesses in spite of large doses of prontosil intramuscularly and sulphanilamide orally.

Toxic signs, viz. cyanosis, nausea and sickness were much more readily induced in puerperal cases than in cases of erysipelas or scarlet fever. This may be accounted for by the more or less profound anaemia present in most of the puerperal patients.

One or two patients developed extensive macular and morbilliform eruptions on the skin, due apparently to the sulphanilamide.

No permanent toxic effects were noted.

It has become the practice in the hospital to treat all puerperal infections with sulphanilamide.

This course appears to me to be justifiable, when some severe cases are greatly improved by the drug and when no serious harm is done to those cases which do not respond to the sulphanilamide.

From the foregoing observations it will be seen that Sulphanilamide has not a uniform action in diseases due to Streptococcal infections. Erysipelas is cured by the drug, while Scarlet Fever is uninfluenced, though both diseases are due to infection with the haemolytic streptococcus. The explanation of this anomaly is probably that Scarlet Fever is due to the toxins elaborated by the streptococcus in a localised focus, whereas, Erysipelas is due in large measure to a widespread invasion of the tissues by the streptococci. Thus streptococcal antitoxin is a more effective remedy in Scarlet Fever than in Erysipelas.

I have shown the inefficacy of sulphanilamide in the cases with abscess formation in the course of erysipelas.

I think it is reasonable therefore to assume that sulphanilamide is only an effective remedy in those cases of streptococcal infection in which the organisms are easily accessible to the drug via the blood or tissue fluids.

Thus streptococcal empyema in the early fluid stages and puerperal blood stream infections should be expected to be amenable to sulphanilamide therapy.

Coliform Bacillus infection of the urinary tract.

10 patients suffering from pyelitis were treated with sulphanilamide. Most of the cases occurred as pyelitis complicating pregnancy. In all the cases coliform bacilli were present in abundance in the urine, and the illness was acute, with pain, high fever and frequency of micturition.

In each instance the usual alkaline treatment had failed to give a permanent cure.

The dose given was ½ gm. of sulphanilamide three times per day.

Within 48 hours of the commencement of treatment there was an improvement in the general condition of the patient and a disappearance of symptoms in every case. This was confirmed in each instance by a disappearance of the coliform bacilli from the urine, as observed microscopically. The rapid change in the microscopical findings in the urine was in fact even more impressive than the clinical improvement.

It was observed however that the treatment in no way lessened the tendency of the disease to relapse.

My impression is that sulphanilamide, in relatively small doses, is a very useful drug in the treatment of pyelitis and cystitis due to infection with coliform bacilli. Though it obviously does not offer a permanent cure for the disease it rapidly clears the symptoms and signs of the acute phase of the illness. Moreover it can be conveniently combined with the usual alkaline

treatment of the disease.

In this series of cases an incident occurred which emphasises the need for strict supervision of patients treated with sulphanilamide.

A woman, aged 25 years, suffering from pyelitis of pregnancy was being treated at home with ½ gm. of sulphanilamide three times per day. She had been warned to take no saline or sulphur laxatives but nevertheless she took a large dose of compound liquorice powder. The following day she became deeply cyanosed, her lips, mucous membranes and finger nails being deep purple in colour. Apart from the cyanosis she was not seriously ill and when the drug was stopped she recovered her normal colour in a few days. At this time she was eight months pregnant. There were no adverse effects on the pregnancy which terminated successfully three weeks later.

Provided the usual precautions are taken, sulphanilamide in the above dosage, is in my experience, as effective and less toxic than Mandelic acid in the treatment of urinary infections with coliform bacilli.

Meningococcal Meningitis.

Four patients suffering from meningococcal meningitis have been treated with sulphonamide drugs during the past 2½ years.

Meningococcal antitoxin (Parke Davis & Co) intrathecally and intravenously has given good results

in former years in the treatment of meningitis and it was thought to be inadvisable to discontinue this method of treatment entirely.

All the cases were treated with completely successful results.

During the two years prior to the introduction of prontosil only two cases of meningococcal meningitis were dealt with a Thornton Isolation Hospital. One case during 1935 made a good recovery and one case during 1936 died.

I shall give details of the four cases treated with sulphonamides.

Case 1.

Arthur Fowler aged 17 years was admitted to hospital on 5/3/37 in his eighth day of illness. On admission he was semi-conscious with nuchal rigidity and squint.

Lumbar Puncture. Cerebro spinal fluid was purulent and under high pressure. 19 c.c. were allowed to run off. Meningococcal antitoxin 15 c.c. were given intrathecally. 20 c.c. prontosil red was given intramuscularly.

As soon as he was able to swallow he was to have ½ gm. sulphanilamide three times per day. Meningococci were found in the cerebro spinal fluid. On 6/3/37 he was much improved, both mentally and physically. Squint had disappeared.

He was given Meningococcal Antitoxin 15 c.c. intravenously and the sulphanilamide by mouth was continued. On 7/3/37 his temperature was normal and remained so thereafter. General condition much improved.
Lumbar puncture - 18 c.c. turbid fluid ran off and he was given Meningococcal antitoxin 5.c.c. intrathecally and 22 c.c. intravenously.

On 8/3/37 - Improving - given 5.c.c. meningococcal antitoxin intravenously.

On 10/3/37 Lumbar puncture gave 15 c.c. of clear fluid under slight pressure. Sulphanilamide was stopped. Meningococcal antitoxin 5 c.c. intrathecally and 10 c.c. intramuscularly given.

On 12/3/37 Lumbar puncture showed cerebro spinal fluid clear. He was given meningococcal antitoxin 4 c.c. intrathecally and 8 c.c. intravenously.

On 16/3/37 Lumbar puncture. Cerebro spinal fluid clear and pressure normal.

On 26/3/37 Lumbar puncture. Cerebro spinal fluid clear and pressure normal. Cells 2 p.cmm.

On 2/4/37 he was discharged fit.

He had a total of 7 gms. of sulphanilamide, 20 c.c. of prontosil red and 102 c.c. of meningococcal antitoxin by various routes.

Case 11.

Wm.Brown, aged 14 years, was admitted to hospital on 12/1/38 at 10 a.m. in his third day of illness. He was unconscious on admission and extremely restless. On admission lumbar puncture had to be done under general anaesthesia.

Cerebro spinal fluid was purulent, 32 c.c.run off under high pressure. He was given meningococcal antitoxin 15 c.c. intrathecally, 10 c.c. intravenously and 5 c.c. intramuscularly.

Soluseptasine 5 c.c. was given intramuscularly. At 8.30 p.m. on same day lumbar puncture was again done under general anaesthesia. 10 c.c. turbid fluid taken off. He was then given meningococcal antitoxin 15 c.c. intravenously and 15 c.c. intramuscularly. Soluseptasine 5 c.c. was given intramuscularly. Morphia was given to quieten him at night.

13/1/38. He was conscious and without eye symptoms, although there was severe headache and nuchal rigidity. Meningococcal antitoxin was given , 10 c.c. intravenously and 3 c.c. intramuscularly. Sulphanilamide ½ gm. four hourly by mouth.

14/1/38. He was much improved. Lumbar puncture now possible under local anaesthesia. Cerebro spinal fluid now much clearer, 28 c.c. taken off under slight pressure.

Meningococcal antitoxin 9 c.c. given intravenously.

15/1/38. Improving. Lumbar puncture.25 c.c. cerebro spinal fluid under pressure but much clearer. Meningococcal antitoxin 10 c.c. given intramuscularly.

16/1/38. Improving. Lumbar puncture. 20 c.c. clear cerebro spinal fluid run off. Meningococcal antitoxin 12 c.c. given intramuscularly.

18/1/38. Now very well. Lumbar puncture. 12 c.c. clear cerebro spinal fluid run off.

1/2/28. Allowed up and sulphanilamide by mouth stopped.

9/2/38. Discharged fit.

Total amount of sulphanilamide given was about 28 gms. 10 c.c. of soluseptasine given during the first day and in all 104 c.c. of meningococcus antitoxin was given by various routes.

Case 111.

George Dickson, aged 17 years, was admitted to hospital on 16/3/39 in his fourth day of illness.

On admission he had definite meningeal irritation with double vision. He was drowsy but could co-operate in the examination.

Lumbar puncture (under local anaesthesia) 45 c.c. purulent cerebro-spinal fluid under high pressure were taken off. He was given meningococcal antitoxin 13 c.c. intrathecally and 17 c.c. intravenously. 2 gms. of M.& B.693 was given by mouth as an initial dose followed by 1 gm. 2 hourly.

17/3/39. Much improved but restless.
Lumbar puncture. 45 c.c. purulent cerebro spinal fluid taken off. Meningococcal antitoxin 14 c.c. intrathecally and 16 c.c. intravenously given.

18/3/39. Lumbar puncture. 25 c.c. less turbid cerebro-spinal fluid run off. Meningococcal antitoxin 14 c.c. intrathecally and 16 c.c. intravenously given.
The M.& B.693 was reduced to 1 gm. 4 hourly.

19/3/39. General condition improved.
Lumbar puncture. 30 c.c. rather less turbid cerebro-spinal fluid run off. Meningococcal antitoxin 15 c.c.given intra muscularly.

20/3/39. Much improved.
Lumbar puncture. 30 c.c. cerebro-spinal fluid run off. Less turbid. 15 c.c. meningococcal antitoxin intramuscularly.

22/3/39. Lumbar puncture.40 c.c. cerebro spinal fluid taken off. Fluid now almost clear.

24/3/39. Now very well generally.
Lumbar puncture. 35 c.c. cerebro spinal fluid, clear but under pressure.

27/3/39. Lumbar puncture. 30 c.c. clear cerebro-spinal fluid taken off. Pressure still above normal.

7/4/39. Cerebro-spinal fluid clear and cells normal.

13/4/39. Discharged cured.

A total of 48 gms. of M.& B.693 was given by mouth, no sulphanilamide preparation given by injection and 120 c.c.of meningococcal antitoxin given by various routes.

This boy's temperature was normal from the eighth day of illness.

Case 1V.

Kathleen McNaughton aged 2 years was admitted to hospital on 3/2/39 in her third week of illness.

There was a history of her having stiffness of neck and weakness of one arm for 2 weeks. Her mother had a simultaneous illness proven to be due to meningococcal infection.

On admission there was definite nuchal rigidity. Lumbar puncture. 30 c.c. slightly turbid fluid taken off under pressure.

This fluid was reported to have the picture of meningococcal meningitis though the organism was not found.
M.&B.693 ¼ gm. by mouth 4 hourly.

4/2/39. Meningococcal antitoxin 20 c.c. given intramuscularly.

5/2/39. Nuchal rigidity still present.
Lumbar puncture. Pressure still increased.
10 c.c. meningococcal antitoxin given intrathecally and 20 c.c. intramuscularly.

6/2/39. No nuchal rigidity.

7/2/39. Lumbar puncture. Pressure of cerebro spinal fluid still above normal.

9/2/39. Lumbar puncture. Pressure of cerebro spinal fluid normal.

20/2/39. M.& B.693 stopped.

4/3/39. Discharged well.

Total amount of M.& B.693 given was about 16 gms. spread over two weeks. There was no sulphonamide given by injection. 50 c.c. of meningococcal antitoxin were given in all.

This, the only case from which the meningococcus was not recovered was of the chronic type. The concomitant meningococcal meningitis in the mother (treated in Perth) and the clinical signs in the child were taken as sufficient evidence to include the case in this series of meningococcal meningitis.

Definite conclusions cannot be based on such a small series of cases. The complete recovery and the rapid amelioration of symptoms and signs in a disease of such gravity suggest that the sulphonamide preparations were of some value in the treatment. On theoretical grounds the combination of the antitoxin with a bacteriacidal drug appears to be the ideal treatment.

In order to establish the value of the drug it would be necessary to omit the antitoxin therapy in a few cases, but, from my experience with sulphanilamide in scarlet fever, I am very reluctant to do so, in such a highly dangerous disease as meningococcal meningitis.

Staphlococcal Infection.

Uleron, a German sulphonamide, was introduced early in 1938 by Bayer Products Ltd.. with the claim that it had a bacteriocidal action against staphlococci in the body. The chemical denomination of this drug is (4-(4amino-benzol-sulphonamido) -benzol-sulphon-dimethyl-amide).

My experience with this preparation is limited to one case only. This is reported here because this patient, suffering from staphlococcal pyaemia presented an excellent opportunity for a clinical trial of the drug.

Mitchell (1938) reported success with the drug in the treatment of five cases of acute osteomyelitis due to Staphlococcus aureus.

I am unable to confirm his good report on the action of the drug.

In August 1937 a man aged 45 years, developed a staphlococcal blood infection following a severe septic finger. He was treated with sulphanilamide ½ gm. four hourly for a week without any improvement in his condition or lessening of the infection.

During the ensuing months he developed abscesses in both arms, in his shoulder, in the lumbar region of the back, in the legs, over the occipital region of the head, and in the left eye. The eye infection resulted in panophthalmitis necessitating enucleation of the eye-ball.

In May 1938 the pyaemia was still present and fresh abscesses were developing in the bones of the legs, arms and skull.

He was now treated with Uleron. He was given a series of short courses of treatment with two or three days between each, as recommended by the manufacturers. The object of this was to avoid toxic symptoms. Each course consisted of 2 gms. of Uleron per day in four doses for 3 or 4 days. In this manner he was given six courses.

No improvement whatever could be recorded and he actually developed fresh abscesses while under treatment with the drug.

The pus from the abscesses was reported to give pure growths of staphlococcus aureus on culture.

It would appear therefore that in this case the Uleron was not capable of killing staphlococcus aureus in the blood stream during the course of the pyaemic process.

This patient is still uncured (August 1939).

During the course of the treatment of this patient with Uleron I formed the opinion that it was a more toxic drug than sulphanilamide. This particular case at least tolerated the sulphanilamide much better than the Uleron.

Ophthalmia Neonatorum.

During the year 1938 fifteen babies with ophthalmia neonatorum were treated with sulphonamide drugs in addition to the standard treatment of irrigation and silver drops. In the first eight months of the year sulphanilamide (streptocide) was used; thereafter the new sulphonamide, M.& B.693 was the preparation used. The daily dose of both sulphanilamide and M.& B.693 was $\frac{1}{2}$ gm. given in three equal quantities.

The babies tolerated the drugs well, there being no appreciable toxic effects either with the sulphanilamide or the M.& B.693.

Only five of the cases were proved to be due to gonococcal infection of the eyes. The other ten cases were reported to have pneumococci or diphtheroid organisms in the purulent discharge from the eyes.

The gonococcal cases all occurred in the early part of the year and were treated with sulphanilamide.

Every case recovered completely without permanent damage to the eyes.

Similar results however have been obtained in previous years.

The time taken for the eyes to become free from pus in those few cases, was not sufficiently reduced from the time taken in cases treated in previous years, to say whether the sulphanilamide influenced the course of the disease or not.

In May 1939 a severe case of gonococcal ophthalmia neonatorum was treated with M.& B.693. The unusually rapid effect of treatment in this instance suggests that the M.& B.693 contributed largely to the cure of the disease.

A female child born on 7/5/39 was admitted to hospital on 10/5/39 with a history of discharge from both eyes since the day of birth.

On admission, weight was $7\frac{3}{4}$ lbs. There was profuse, thick, yellow, purulent discharge from both eyes. The eyelids of both eyes were red and oedematous. Both corneae were hazy.

The baby was admitted in the afternoon and during the same evening was given two doses of M.& B.693, each $\frac{1}{6}$gm. The eyes were instilled with lunosol drops once that day and irrigated with boric lotion two hourly.

During the night the eyes were severely inflamed and were discharging profusely.

At 6 a.m. the following morning both eyes were noted to improve markedly and from this time the discharge was very scanty and watery in type, although the eyelids were still red and swollen. The M.& B.693 was continued - $\frac{1}{6}$ gm. t.i.d.

On the morning of the 14/5/39 both eyes were completely free from inflammation and discharge. On the same evening the baby had some cyanosis and the M.& B.693 was discontinued. The total quantity given was

2½gms.

The baby was discharged, cured, on the morning of 18/5/39.

Thornton Isolation Hospital has been the centre for treatment of all cases of ophthalmia neonatorum occurring in the County of Fife for the past ten years. In the hospital it has never been known for a proven gonococcal ophthalmia to be free from purulent discharge within 24 hours of admission to hospital.

This case would indicate that M.& B.693. is the most valuable treatment for gonococcal ophthalmia yet tried, and certainly superior in this respect to sulphanilamide.

This drug will certainly be the sulphonamide of choice in the treatment of gonococcal infections of the eyes.

Para-typhoid Fever.

Three patients convalescent from enteric fever, due to infection with B.paratyphosus B., were found to be in the carrier state. The usual remedies had failed to clear the faeces of pathogenic organisms.

In each case sulphanilamide, ½ gm. every four hours, was given for a week and the faeces again examined. B.paratyphosus B. was recovered from the faeces in each instance.

One of those patients had also been treated with

sulphanilamide during the acute stage of the disease, without effect on the fever or the toxaemia.

Those cases are included because it has recently been reported that sulphanilamide may be of value in the carrier state of enteric fever (Cookson 1939)

Pneumonia.

In July 1938 Evans and Gaisford reported notable success in the treatment of pneumonia with the latest sulphonamide, 2-(p-Aminobenzenesulphonamido)-pyridine or M.& B.693. Their work was the sequel to Whitby's discovery that in 'in vivo' experiments with mice, M.& B. 693 had a lethal effect on pneumococcal cultures.

At Thornton Isolation Hospital from 60 to 90 patients suffering from pneumonia are treated annually. Those patients, I find, are removed to hospital mainly for two reasons, viz.(1.) In the course of the illness the patient has become critically ill,or, (2) the patient's home is too poor to provide sufficient accommodation and material for proper nursing.

The patients admitted to hospital then are usually acutely ill and many of them are suffering from defective nutrition.

Those factors combine to produce a heavy mortality in patients suffering from pneumonia, met with in hospital practice.

During the past few years the mortality figures

for patients of all ages suffering from all types of pneumonia have been:-

During 1935, - 65 cases treated with a mortality of 14%
" 1936, - 87 " " " " " " 24%
" 1937, - 84 " " " " " " 13%
During first 7 months of 1938, 73 cases treated with a mortality of - 19%

Those figures are closely similar to mortality rates found among hospital patients suffering from pneumonia in various parts of the Country. Thus Evans & Gaisford quote the rate at Selly Oak Hospital, Birmingham as 25.6%, that at Middlesex and Royal Free Hospitals, London, as 19% and that at Dudley Road Hospital for the past two years as 27.8%

In private practice and in healthy individuals there is no doubt that the mortality rate is much lower. In Osler & McCrae's textbook on the Practice of Medicine 6% is quoted as the mortality rate in a large series of private patients. It is also quoted that in 40,000 cases of pneumonia in the German Army the death rate was 3.6%.

It is of course generally recognised that the mortality rate in pneumonia varies more with the age than with any other single factor. Thus at the Royal Hospital for Sick Children, Glasgow, the mortality rate varied from 65% in infants under 6 months to 3% in children between the ages of 10 and 14 years (L.Findlay in Thomson's 'Sick Children') and over the age of 60 years

the mortality may be as high as 80% (Beaumont & Young in Price's Textbook of Medicine).

Another extremely important factor bearing directly on the mortality rate in pneumonia is the type of pneumococcus with which the patient has become infected.

The patients being treated at Thornton Isolation Hospital are of all ages from the very young to the very old, though the great majority of the patients are children or young adults.

So far it has not been possible to carry out any investigation of the incidence of the various types of pneumococci in the cases of pneumonia treated.

In August 1938, I decided to use the new drug M.& B.693 in the treatment of pneumonia. At first, my intention was to treat only every second case with the M.& B.693. in order to have a concurrent series of cases for controls. This scheme was abandoned, however, in a very short time. The treated cases were noted to improve so rapidly, that it was felt to be wrong to withhold the treatment in control cases which were desperately ill. For example, in three children (nos. 60, 62 & 66 in the series) aged 13 months, 2 years and 2½ years, all ill with broncho-pneumonia, the M.& B 693. was withheld for 6 days, 3 days and 6 days, respectively, during which time they had high fever and were acutely ill. In each case when the course appeared to be becoming unfavourable M.& B.693 was given and

within 24 hours the temperature was normal and the toxaemia abated.

Experiences such as those make it difficult to keep rigorously to scientific methods when dealing with a highly fatal disease such as pneumonia.

It was therefore decided to treat every case admitted with pneumonia with M.& B.693.

During the past year there were 66 cases of pneumonia treated in hospital with M.& B.693.

This series included patients of all ages from 3 months to 70 years. There were 24 patients of 2 years of age and under, there were 28 patients between the ages of 2 years and 30 years, and there were 14 patients over 30 years of age.

34 of the patients had pneumonia of the lobar type and 32 had broncho pneumonia or lobular pneumonia. In the descriptive list of patients given below, the patients are grouped according to the type of pneumonia. This however is of little importance because it is often extremely difficult to be certain clinically which type of pathological process is taking place in the lung.

All of the patients in the series were suffering from pneumonia with definite signs and symptoms. Patients who were notified and admitted as pneumonia and later found to be suffering from bronchitis, influenza, tuberculosis etc. were not included in the series, though in many cases they also were treated with M.& B.693.

By this selection, there were no fatal or unsuccessful cases excluded from the series.

The routine fresh air treatment was continued as in former years. Prior to August 1938 I gave three daily doses of a mixed pneumococcal, streptococcal and influenzal vaccine to patients admitted within 48 hours of the onset of illness. This was discontinued in the present series of patients.

X Ray examination was not used in diagnosis as this is impracticable at Thornton Isolation Hospital.

No bacteriological investigations of the cases was done, i.e. neither examination of the sputum nor typing of the infecting pneumococci. This would undoubtedly have been desirable. There are no laboratory facilities within 20 miles of the hospital however and the exigencies of general practice made it impossible for time to be spent in typing pneumococci at the bedside.

The dosage of the M.& B. 693 which was adopted in this series, was based on the recommendations of Evans & Gaisford. It was modified in individual cases according to my previous experience with sulphanilamide.

An adult was given 2 gms. on admission followed by 1 gm. every four hours for two days. Thereafter if the reaction was favourable, the dose was reduced to ½ gm. four hourly and gradually reduced further with clinical improvement. In no case was the drug stopped

till a few days after the patient became afebrile.

The dose was halved in cases of children of the school age and quartered for younger children.

In every case the drug was given by mouth. The total quantity given to each patient depended on the severity of the disease, the tolerance of the individual to the drug and the response to treatment.

There were 5 deaths in the 66 cases of pneumonia treated with M. & B.693, giving a mortality rate of 7.6%.

The following table gives the mortality in the three age groups.

Age Group of Patients	2 years & under.	From 2 years to 30 years.	Over 30 years	Total all ages.
No.of patients in each group	24	28	14	66
Mortality rate in each group	8%	nil.	21%	7.6%

Details of the five fatal cases are as follows.-

1. A frail,old lady of 70 years, Her pneumonia was of the hypostatic type and she was afebrile from the time of admission. She died three days after admission.

2. A child of 4 months, admitted on the 9th day of illness with broncho pneumonia. She was given $\frac{1}{4}$ gm. of M.& B.693,4 hourly. She gradually became worse and 36 hours after admission developed convulsions and died an hour or so later.

3. A marasmic child of 6 months admitted on the fourth day of illness with broncho pneumonia. He was given

½ gm. M.& B. 693 on admission and ¼ gr,. four hourly thereafter. He died three days after admission. The temperature was in the region of 101°F - 104°F. throughout and there was apparently no response to the drug.

4. A man, 50 years of age, admitted to hospital on his 7th day of illness with broncho pneumonia at both bases. He was given 1 gm. of M.& B.693 four hourly. He was delirious and extremely restless from the time of admission. Morphia was required as he could not be kept in bed. He gradually became worse and died 24 hours after admission, having had 5 gms. of M.& B.693.

5. A man of 60 years admitted on his 4th day of illness with pneumonia of the lobar type. At the end of 24 hours during which time he had 5 gms. of M.& B.693 his temperature was normal but his pulse rate had increased. He had a heavy cloud of albumin in his urine. He gradually became weaker and died 60 hours after admission.

Post mortem examination was not carried out in any of the fatal cases.

The comparatively low mortality rate of 7.6% gives the most concrete result of the administration of M.& B. 693 to cases of pneumonia.

Early in the course of the experiment, however, after a few acutely ill patients had been treated, there was very little doubt in my mind as to the value of the drug. In the great majority of cases 36 to 48 hours of treatment was sufficient to produce a dramatic improvement in the condition of the patient somewhat resembling the crisis in the ordinary course of lobar pneumonia. This occurred, however, irrespective of the stage of the disease and not, as usually occurs, always about the 7th day of illness. Thus in 48 patients in the series defervescence occurred within 48 hours after

treatment with M.& B.693 was instituted. In the 34 typical lobar cases 29 patients responded to treatment within 48 hours in this way.

The first indication of a favourable result was usually a lessening of the toxaemia. The fall in temperature and pulse rate and the improvement in physical signs were usually more gradual than is seen at the crisis in a typical case of lobar pneumonia. The pulse rate and the respiratory rate improved more slowly than the temperature, and frequently took one or two days to return to normal after the patient had become afebrile. This lag in the fall of the pulse and respiratory rates is explained clinically by the fact that the lung consolidation was noted to take several days to clear following the first improvement in the patient. In one or two cases, treated early, a gradual improvement of symptoms simultaneous with an increase in the consolidation of the lung was observed during the first few days. This anomaly seemed to indicate that although the pneumococcal growth and therefore the toxaemia had been checked, the pathological changes in the lung continued in their usual sequence viz. congestion, consolidation and resolution.

This is a matter of great importance I think in the conduct of the case. While the lung is still solid and the pulse rate higher than normal it is essential to restrain the patient from exerting himself unduly.

This may be a real difficulty in a patient who has not been ill long enough to be in the extremely weak state seen subsequent to the ordinary crisis in lobar pneumonia and who has been given complete relief from severe symptoms. In hospital practice it is easy to ensure that sufficient rest is enforced but this is not always so in private practice when the patient is not being attended by competent nurses.

This danger was illustrated by Case No.4. a boy, strong and healthy, 21 years of age, He was the only patient treated at home in the series described.

On his 2nd day of illness when treatment was commenced he had severe pleurisy at the right base with temperature 103° F., cough, and blood stained sputum. There was impaired percussion at right base, friction sounds and diminished air entry.

On the 3rd day he was much improved but there was now definite consolidation of the lung at the right base.

On the 4th day the temperature was normal and remained so.

The consolidation persisted till the 6th day when he was feeling so well that he got out of bed.

About the 10th day he complained of pain in the right lower chest again and signs of fluid were now present. He had no elevation of temperature and he felt very well otherwise.

About 5 c.c. of straw coloured fluid were aspirated

and the chest cleared spontaneously with rest in ten days time.

In my opinion the boy's pleural effusion resulted from excessive exercise before sufficient time had been given to allow resolution to take place.

The danger of such a condition is of course simultaneous infection of the fluid with organisms and the possibility of the development of empyema.

In the following tables the patients are grouped according to the type of pneumonia from which they suffered. Thus No's 1 to 34 were all more or less typical cases of lobar pneumonia: No's 35 to 66 were of the bronchopneumonic type.

The patients are also grouped according to the day of illness on which treatment with M.& B.693 was instituted. The frequency with which the drug produced rapid improvement and fall in temperature is thus clearly seen.

Patients with Lobar Pneumonia.

No.	Day treatment began	1st day afebrile	Age	Total M&B 693	Results.
1.	2nd day	4th	52	25 gms.	Cured.
2.	"	3rd	19	8 "	"
3.	"	4th	28	18 "	"
4.	"	4th	21	10 "	Pleural effusion. Aspirated Spontaneous absorption.
5.	3rd day	4th	2½	8 gms.	Apical pneumonia. Acutely ill on admission. Cured.
6.	"	4th	3	8 "	Apical pneumonia. Acutely ill on admission. Cured.
7.	"	7th	21	23 "	Extremely ill on admission. Dense dullness right base. Cured.
8.	"	4th	34	16 "	Cured.
9.	"	8th	3½	16½ "	Cured.
10.	4th Day	6th	11	11 "	Cured.
11.	"	5th	12	6 "	Cured.
12.	"	5th	60	5 "	Temp.fell in 24 hours. Pulse rate increased. Died 60 hours after admission.
13.	"	5th	6	6 "	Cured.
14.	"	6th	2¾	7½ "	Cured.
15.	"	6th	17	13½ "	Cured.
16.	"	6th	44	25½ "	Cured.
17.	"	5th	5	11 "	Cured.
18.	"	6th	26	25½ "	Cured.
19.	"	5th	7	6½ "	Cured.
20.	"	6th	16½	1 gm. t.i.d.	Temp.rose on 8th day and in spite of M&B.693 she had irregular temp.and spreading pneumonia for 4 weeks. Final cure by lysis.
21.	"	5th	42	15gms.	Cured.
22.	"	5th	11	6½ "	Cured.

No.	Day treatment began.	1st day afebrile.	Age	Total M&B 693	Results.
23.	5th	10th	5	¼ gm. t.i.d.	This was an early case in the series & I do not think had a big enough dose. Cured.
24.	"	6th	11	9 gms.	Cured.
25.	"	6th	17	14 "	Cured.
26.	"	7th	17	29 "	Acutely ill & delirious on admission. Delirium clear in 12 hrs. Cured.
27.	"	6th	65	12 "	Cured.
28.	"	6th	39	62 "	Chronic bronchitis also. Relapse on 8th day & temp. did not fall then till 16th day. Cured.
29	6th	7th	54	14½ "	Cured.
30.	"	7th	14	5½ "	Cured.
31.	"	7th	4	5 "	Cured.
32.	"	7th	41	17 "	Cured.
33.	7th	9th	10	10½ "	Cured.
34.	"	11th	23	21 "	Cured.
Patients with Broncho Pneumonia.					
35.	2nd	afebrile	70	1 gm. 4 hrly.	Died. Hypostatic pneumonia.
36.	"	4th	2	5 gms.	Cured.
37.	"	3rd	1	3¾ "	Cured.
38.	3rd	5th	1½	5 "	Suffering also from severe rickets. Cured.
39.	"	4th	2	4½ "	Cured.
40.	"	5th	1½	5 "	Cured.
41.	"	20th	37	38 "	Broncho-Pneumonia occurring in an old tuberculous chest. No effect.
42.	"	8th	78	21 "	Cured.
43.	"	5th	61	10 "	Cured.
44.	"	8th	8½	9 "	Cured.

No.	Day treatment began.	1st day afebrile.	Age	Total M&B 693	Results.
45.	3rd	8th	8/12	7¼ gms.	Cured.
46.	"	5th	1½	3 "	Cured.
47.	4th	6th	1 8/12	9½ "	Cured.
48.	"	6th	1	6 "	Cured.
49.	"	5th	1	6 "	Cured.
50.	"	7th	½	5 "	Cured.
51.		-	½	6 "	Marasmic child. Died on 7th day. No effect on temperature.
52.	5th	7th	23	9 "	Pneumonia cured. Suffering also from asthma.
53.	"	13th	2	30 "	Cured.
54.	"	7th	4/12	10 "	Cured.
55.	"	7th	½	6½ "	Cured.
56.	"	12th	¼	10¼ "	Badly undernourished child. Cured.
57.	"	7th	8/12	5¾ "	Cured.
58.	6th	8th	2	10¼ "	Cured.
59.	"	9th	5/12	3¼ "	Cured.
60.	7th	8th	1 4/12	5¾ "	M&B 693 withheld for 6 days. Cured.
61.	"	-	50	5 "	Extreme delirium & restlessness. Died 24 hours after admission.
62.	"	8th	2	6 "	M&B 693 withheld for 3 days. Cured.
63.	8th	10th	5/12	9 "	Cured.
64.	9th	-	4/12	2 "	Died 36 hrs. after admission. Terminal Convulsions.
65.	"	20th	24	30 "	Unresolved pneumonia. Discharged well.
66.	"	10th	2½	10½ "	M&B 693 withheld for 6 days. Cured.

Complications due to Pneumonia.

The case (No.4) already quoted was the only patient in the series who had complications directly the result of the pneumonia.

For comparison I shall give the number of complicated cases in previous years.

1938.

In the early part of the year of 73 cases of pneumonia 4 patients developed empyema. All 4 were of pneumococcal type. Two adults were treated by rib resection, one adult by aspiration and the fourth case, a child, was treated by insertion of a cannula. All four were cured.

1937.

Of 84 cases, 5 developed empyema.

1. Man, aged 64 years. Pneumococcal empyema. Rib resected. Good result.
2. Boy, Aged 16 years. Pneumococcal empyema. Rib resected. Died of septicaemia later.
3. Man, aged 30 years. Streptococcal empyema. Rib resected. Cured.
4. Man, aged 26 years. Streptococcal empyema. Cured with aspiration and sulphanilamide.
5. Child, 15 months. Staphlococcal empyema. Drained with cannula. Cured.

1936.

Of 87 cases of pneumonia one child developed empyema. This was of pneumococcal type and was cured by drainage with a cannula.

It is my opinion that patients suffering from pneumonia and treated with M.&B.693 will run grave risk of empyema developing if they are allowed out of bed before the 10th day of illness.

Though in the majority of cases of both types of pneumonia a beneficial effect was observed, there were cases both of lobar and broncho-pneumonia which were apparently unaffected by the drug or only temporarily improved. Cases Nos.20, 25, 28, 41, 56 and 65 illustrate that the drug is not invariably successful. In cases 20 and 23 the dose may have been insufficient. Both occurred early in the series before the routine dosage was stabilised.

Case No.28 was a chronic bronchitis. His temperature fell on the 6th day, rose again on the 8th day and remained elevated till the 16th day in spite of continuous administration of M.& B.693, and in spite of the fact that there was no clinical evidence of pus collecting in the chest. The ultimate improvement was by lysis.

Case No.41 had a broncho-pneumonia superimposed on a previously tuberculous chest. The drug had apparently no effect.

Case No.56 was a poorly nourished infant.

Case No.65 admitted on the 9th day had apparently an unresolved pneumonia. The M.&B.693 had no effect in reducing the fever, which subsided by lysis on the 20th day, 11 days after admission.

There is no doubt that further bacteriological investigation is necessary and this may reveal that certain types of infecting organisms are resistant to the bacteriocidal effects of M.&B 693.

Another explanation of the resistant cases is suggested by my experience with sulphanilamide in erysipelas. It may be that the drug cannot reach the infecting organisms in sufficient concentration, when the infected area becomes partially walled off from the blood or tissue fluids, as might well happen in collections of pus in the chest, empyema, lung abscess or in fibrosed areas of the lung as in a tuberculous lung or an unresolved pneumonia.

A case which is not included in the above series and which is still in hospital may lend support to this theory.

A boy of 14 years, thin and nervous, with a previous history of bronchiectasis was admitted to hospital on the 2nd day of his illness. He was acutely ill and had all the signs and symptoms of pneumonia at the right base. He was given 1 gm. of M.&B.693 followed by ½ gm. four hourly. He improved and his temperature fell to normal on the fourth day of his illness. On the fifth day the temperature rose again and although he was not now acutely ill he remained fevered in spite of continuous M.& B.693 administration. By the 11th day there was a localised patch of dullness

about 3" in diameter in the post-axillary line at the right base.

The chest was explored in this region and 10 ounces of thin purulent, fœtid pus was withdrawn. Aspiration was repeated two days later and five days later a cannula was inserted as the pus was becoming thicker.

The only organism grown from the pus was the pneumococcus and this in spite of continuous M.&B.693 administration for a total amount of 25 grammes.

This pneumococcus must have been either resistant to the drug or the drug was unable to get into contact with the organisms in sufficient concentration.

From my experience, I have concluded that when the M.&B.693 does not give a prompt response in the treatment of pneumonia it is wise to regard the case as either being a potentially complicated one, or having had the pneumonia super-imposed on some pre-existing chronic disease.

Toxic effects attributable to the M.&B.693 were remarkably rare. The precautions of giving patients only a light, sulphur free diet and avoiding saline cathartics, which are now part of the routine in all sulphonamide therapy, Douthwaite (1939) were observed in all the cases of the series.

Nausea and sickness occurred in a few cases but never of sufficient severity to upset the patient seriously, or to make administration by mouth difficult.

Cyanosis occurred more frequently. This was regarded as evidence of overdosage or of idiosyncrasy of the patient to the drug and was taken as an indication for the dose to be reduced. In no case was the cyanosis accompanied by harmful effects to the patient, and if the pneumonic condition had not subsided it was always possible to continue with the drug in reduced dosage.

It is noticeable that M.&B.693 has less tendency to produce cyanosis than sulphanilamide.

The cyanosis is now regarded as an excellent warning signal of possible over dosage with no harmful significance in itself.

Babies and children were found to tolerate the M.&B. 693 very well indeed. Elderly patients tended to show cyanosis early and required to be watched carefully for toxic symptoms.

There was no evidence of renal damage resulting from the M.&B.693 treatment.

It was not possible to carry out routine white blood cell counts or to investigate the nature of the changes taking place in the blood when cyanosis developed.

From the series of cases of pneumonia discussed, it appears to me to be reasonable to conclude that M.&B.693 is of great value in the treatment of pneumonia. The simplicity and safety with which it can be administered and the prompt and effective relief given to the patient

make M.& B.693 therapy the method of choice in treating pneumonia of all types. There may, however, be a grave danger of the efficacy of the drug producing an unjustifiable relaxation of the vigilant supervision which is still necessary in every case.

Summary and Conclusions.

1. The results of treatment of a series of 224 cases of scarlet fever with sulphanilamide have been reviewed and compared with a concurrent series of 338 cases of scarlet fever treated without sulphanilamide.

There is no evidence that the sulphanilamide had any beneficial effect in this disease whatever, either in the acute febrile stage or on the incidence of complications.

2. 54 cases of Erysipelas were treated with sulphanilamide with successful results. The toxaemia and the diffuse inflammation respond quickly to the drug.

Attention is drawn to the fact that localised abscess formations are resistant to the effect of the drug.

3. 3 cases of Streptococcal empyema are described. In two cases treated with sulphanilamide by mouth aspiration was sufficient to cure the condition. In one case, treated with proseptasine, (benzyl sulphanilamide) the patient was benefited, but the pleural cavity required to be drained by the operation of rib resection.

Sulphanilamide given early will tend to lessen the frequency of, or, even abolish, the need for operative interference other than aspiration.

4. In 40 cases of puerperal infection excellent results

have been obtained in some cases treated with prontosil rubrum and also in other cases treated with sulphanilamide.

Cases of puerperal infection unaffected by large doses of both of those drugs have also been met with.

Bacteriological investigation of the cases would probably have explained the variation in results.

Where laboratory facilities are not available the use of the drugs in every severe case of puerperal infection is justifiable.

5. In 10 cases of Pyelitis due to infection with coliform bacilli rapid relief of symptoms + disappearance of B.coli from urine was obtained with relatively small doses of sulphanilamide.

This drug does not prevent relapses but can be conveniently combined with alkaline treatment.

6. Sulphanilamide had no curative effect on 3 faecal carriers of Bacillus para-typhosus B.

7. 4 Cases of Meningococcal meningitis treated successfully with sulphanilamide or M.& B.693 and meningococcal antitoxin are recorded.

The impression was formed that the chemotherapy contributed to the success of the treatment.

8. 5 cases of Gonococcal ophthalmia neonatorum were treated with sulphanilamide with equivocal results. One case treated with M.& B.693 was cured dramatically.

9. Uleron was used in the treatment of one case of Staphlococcal pyaemia without success.

10. 66 cases of pneumonia of various types were treated with M.& B.693. The mortality rate in the treated cases was 7.6% From 1935 to July 1938 the mortality rate in pneumonia patients in the hospital was 18% in 309 cases.

Chemotherapy with M.& B.693 is the best available treatment of pneumonia of all types.

The M.& B.693 is not invariably successful. The unsuccessful cases may be due to a highly resistant infecting organism or to a partially encysted infected area, e.g. lung abscess.

The introduction of sulphonamide chemotherapy marks an important advance in the treatment of pneumonia, streptococcal diseases due to bacterial invasion of the body, such as erysipelas, puerperal sepsis and streptococcal empyema, and probably also in the treatment of meningococcal meningitis and gonococcal ophthalmia.

The efficacy of the drugs by mouth simplifies treatment.

Toxic symptoms are relatively few. Cyanosis which frequently develops during treatment is an excellent indication for caution as regards dosage. Patients being treated with the drug should be under supervision. Ambulant treatment is contra-indicated on account of the vertigo, tremor and nervousness which may be produced by the drug.

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