THE TREATMENT OF ACUTE LOBAR PNEUMONIA WITH M & B 693

Fraser Sinclair
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## The Treatment of Acute Lobar Pneumonia with M & B 893

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INTRODUCTION

The subject of this thesis is the treatment of acute lobar pneumonia with the new sulphonamide drug 2-(para amino benzene sulphonamido) - pyridine or 2 - sulphanilyl-aminopyridine, which has been variously named Dagenan, M & B 693 and sulphapyridine. Throughout this thesis the designation M & B 693 will be employed, as it appears to be the one by which the drug is best known in this country. The importance of this disease as a cause of death needs little emphasis. The Registrar-General's returns for England and Wales in 1937, showed that in that year it was responsible for the death of no fewer than 10,061 people. Any means therefore, that can be developed to decrease its mortality, will definitely improve the average prospect of a long, healthy and useful life. Lobar pneumonia is not a rarity. It is a common disease, and any new method of coping with its ravages is not of mere academic interest, but will save many hundreds of lives every year.

Until about ten years ago, acute lobar pneumonia was one of the diseases for which there were no proven specific remedies. Many and varied were the drugs which were supposed to have a special power of combating the disease, but none of them stood up to the test of controlled scientific investigation. Quinine in various forms, strychnine, digitalis and many other drugs all had their staunch supporters, but actual statistics showed that they had little or no value. The medical profession were forced to admit that nursing saved their pneumonia patients, and that they themselves could only treat symptoms as they arose.

At last there came an undoubted advance. Anti-bacterial
sera, effective against types 1 and 2 pneumococci, were produced and given extensive clinical trials, which proved that the prognosis of cases treated with those sera was much better than that of those treated without. This was a great step forward, because about 40% of cases of acute lobar pneumonia are due to those types (Cecil 1937 a). With the passage of time these sera have been steadily made more concentrated and effective, and in the last few years other sera, effective against types 5, 7, 8 and 14 pneumococci, have been elaborated. Of all the sera, type 1 has always been by far the most effective.

Unfortunately there are difficulties and objections in the way of the use of these sera, and, especially in this country, they have not been widely employed. In the first place, they are expensive, the cost of treating an average case being about £10. Secondly, their scientific use involves the typing of the infecting organism in each particular case. Both of these facts make the use of sera in general practice almost impracticable.

The use of a polyvalent serum, effective against types 1 and 2 pneumococci, is only a compromise, and is obviously not satisfactory. Apart from these objections, there is always the risk of anaphylaxis and serum sickness, common to the use of all sera. This can be minimised to a large extent by careful tests for sensitivity but this introduces another complication into treatment.

The conclusion to which one is led is that effective serum treatment involves the speedy admission of the patient to a hospital where a bacteriological examination of the sputum can be carried out. In recent years in America, and to a small extent
in this country, this ideal was being attained, and no doubt in
time to some cases of pneumonia would have been rushed into
hospital, much as a perforated duodenal ulcer is at present.
However, other factors entered the field.

In 1932 Mietzsch and Klarer discovered a substance to
which the name Prontosil was given. This was later changed to
Prontosil rubrum to avoid confusion with two other distinct
compounds to which the name Prontosil was also applied. It is
an azo dye containing a sulphonamide group, and was found to have
a very marked curative effect in infections due to the
Streptococcus pyogenes.

Ever since Ehrlich's discovery of salvarsan in 1906
scientists all over the world had been searching for other
compounds with comparable effects against organisms other than
the Treponema pallidum. This was the first major success. Once
a start had been made combined research in many countries soon
led to other advances. It was discovered that the dye stuffs owed
their activity entirely or mainly to the sulphonamide portion of the
molecule being broken down in the animal body to a much simpler
compound para amino benzene sulphonamide, also known as sulphanilamide.
This resulted in a wide-spread use of sulphanilamide itself and of
various of its derivatives, such as Proseptasine and Soluseptasine.
Chemotherapy had become established, and its tremendous possibilities
were quickly realised.

One of the next lines of research that naturally suggested
itself, was the extension of this new weapon to attack organisms
other than the Streptococcus. It was soon discovered that the
sulphonamide group of drugs was also effective against the Meningococcus, the Gonococcus and the coliform organisms. Against the pneumococcus, however, these first drugs were almost useless, with the exception of some degree of activity against type III.

Many allied substances were investigated, and of a number synthesised in the research laboratories of Messrs. May & Baker Ltd., a compound, 2-sulphanilyl-aminopyridine, discovered by Dr. A. J. Ewins and Mr. M. A. Phillips, in 1937, was found by Whitby in 1938 to possess a high degree of activity against pneumococci of different types. The substance was also found to be effective against streptococci and meningococci. It was issued for clinical trial under the designation T.693, and in September of that year was placed on the market as M & B 693.

It was the effect of this drug on cases of acute lobar pneumonia that I decided to investigate in September 1938. I had just been appointed Senior House Physician at the Western General Hospital, Edinburgh, and was sure that there I should have excellent opportunities for such an investigation. Professor Stanley Davidson, the Medical Director of the hospital, very kindly consented to all the pneumonia cases being put under my care, under the supervision of Dr. McCrie, the Sub-Director, and of the Assistant Physicians, Drs. Easton and Bruce. During the six months that I was in the hospital I encountered 23 undoubted cases of acute lobar pneumonia, and these were treated with the drug. The results from the basis of my thesis.

In my short series of cases I had the very good fortune to encounter four in which the only organism which could be found in the sputum was a Staphylococcus aureus, and one in which only
the Pneumobacillus of Friedländer appeared. The part which these organisms play in the causation of acute lobar pneumonia, and the effects of the drug on them, are fairly fully discussed.

As a preliminary to presenting my cases, I have discussed the symptomatology, pathology and bacteriology of acute lobar pneumonia, with especial emphasis on the bacteriology, and have reviewed the development of the sulphonamides and the theories as to their mode of action.

I had the facilities of an excellent laboratory and am very grateful to the Radiology Department for the willing cooperation that I received.
The Bacteriology, Symptomatology and Pathology of Acute Lobar Pneumonia

Before beginning this section I wish to acknowledge the great help which I have had from three books, my references to which are too numerous to give in detail. They are "The Diagnosis and Treatment of Pneumonia" by Campbell P. Howard, "The Biology of Pneumococcus" by Benjamin White, and "A System of Bacteriology. Part II", published by the Medical Research Council.

**Bacteriology**

Pneumonia has been known and recognised as a disease from the most ancient times, there being several descriptions of its signs and symptoms in Greek and Roman literature. The actual physical signs of consolidation were not, however, discovered until Auenbrugger in 1761 described the typical dullness on percussion and Laennec in 1819 with his newly invented stethoscope first heard bronchial breathing.

Interest in the disease was really stimulated when the science of Bacteriology arose, and the organismal cause of the condition realised. As early as 1875 Klebs found pneumococci in the lungs of men who had died from lobar pneumonia, but he did not realise their significance, and called them "monadines." In 1881 Pasteur and Sternberg, working separately, for the first time isolated the pneumococcus by animal passage, Pasteur using the saliva from a child suffering from rabies and Sternberg normal saliva. Pasteur noticed the capsule, but neither of them realised the connection which the organism had with pneumonia.

In 1882 Friedländer found diplococci in the secretion and
sections of lungs of 8 fatal cases of pneumonia, and in 1883 claimed to have found the same diplococci in the alveolar exudate in all but a few of fifty cases of pneumonia. He also noticed the capsule, mentioned that he thought it was most prominent at the highest stage of the cells existence and was not just a passive precipitate. He also, however, failed to connect the organism definitely with the disease. (Friedländer 1883). To him, nevertheless, should go the credit for being the first definitely to isolate and culture the pneumococcus. At the same time he discovered the bacillus which bears his name, and which also plays a part in the causation of pneumonia.

To Albert Fraenkel, it is generally agreed, goes the honour of being the first man to state that he believed the pneumococcus was the cause of pneumonia. He first entered the field in 1884, when he claimed to have discovered the diplococcus before Friedländer (Fraenkel 1884). In 1886 he suggested that the pneumococcus as found in pneumonia and the organism found in saliva by Pasteur and Sternberg were one and the same, and also definitely stated that the pneumococcus was the cause of pneumonia. (Fraenkel 1886).

The next advance came when Weichselbaum disagreed that the pneumococcus was the sole cause of pneumonia, which he separated into lobar croupous, lobular and hypostatic types, and said that it caused the lobar type, while streptococci, staphylococci and Friedlanders bacillus caused the other types. (Weichsalbaum 1886).

The next ten years marked the beginning of the attempt to find a serum treatment for pneumonia. Foa and Bordoni - Uffreduzzi in 1886 managed to actively immunise rabbits, but failed to apply the results to human infections. (Foa and Bordoni - Uffreduzzi 1886).
In 1891 the Klemperers made a considerable advance when they found that an immune body appeared in the serum of rabbits just before the crisis, which conferred a passive immunity upon other rabbits when injected into them. They tried their serum out with some success on six human patients, and thought that they had found an antitoxin for the pneumococcus.

The next step was the observation of the phenomenon of agglutination of pneumococci in immune sera. This was first noted by Metchinkoff in 1891 (Metchinkoff 1891), and verified and named in 1897 by Besancon and Griffon, who concluded from their observations that from the standpoint of agglutination there existed several races of pneumococci, which behaved as though different microbes. (Besancon and Griffon 1897). This was the basis of the subsequent classification of the pneumococcus into serological types, and the treatment of the disease by type specific antisera.

It was not, however, until 1910 that Neufeld and Haendel suggested that there were many types of pneumococci, all with specific antisera, and that the aim of treatment should be to "type" the infecting organism by its agglutination with specific serum and then to give therapeutically the type specific antiserum.

From 1910 until 1938 innumerable workers elaborated this classification of the organism into types, and repeated attempts were made to produce effective type-specific antisera, with considerable success for certain types. In 1938 the position was that thirty types of pneumococci had been differentiated. Originally thirty-two had been described, but later work showed that type twenty-six was identical with type six, and type thirty with type fifteen. (Noble
and Cameron 1939). The simplest and most effective method of typing was agreed to be the Neufeld agglutination reaction, using mouse inoculation if the organisms were scanty in the sputum. An antiserum of undoubted clinical value had been produced to combat type one pneumococcus, another not as effective, but still very helpful against type two, and work was being pushed forward in obtaining sera potent against type 3 and the various pneumococci in group four.

The discovery in 1938 that M & B 693 was active against different types of pneumococci, and subsequent confirmation, that it was active against all types as well as against a number of "untypable" varieties, would appear to lessen the value of this work, as regards its bearing on the therapeutic use of type-specific sera. However, it is believed by some workers, (e.g. Fleming 1939. De and Basu 1938, Loewenthal 1939), that the best results may follow the use of combined chemo- and sero-therapy. In addition, with any type of pneumococcus, strains may be encountered which are resistant to M & B 693. In these infections type-specific serum might be invaluable, unless an alternative chemotherapeutic agent becomes available to which the resistant strains might prove susceptible.

A short review will now be given of the characteristics of the pneumococcus and mention will be made of the other organisms causing acute lobar pneumonia. The actual changes found in the body in the disease will also be referred to briefly.
Pneumococcus

This organism is by far the commonest cause of acute lobar pneumonia. Price's Textbook of Medicine states that most cases are caused by the organism, while Cecil (1927) in New York found that 95% of his 2000 cases were due to the pneumococcus. In a recent survey Bullowa and Gleich (1938) of the Harlem Pneumonia Hospital, New York, found that the organism was responsible in 3065 of 3573 cases.

The organism is present in the saliva of from 80 - 90% of normal people, even in its virulent forms, and in pneumonia is found in the bronchial and alveolar exudate. In this disease it is also found in the blood in a high proportion of cases, some workers (Prochasta 1900, Rosenow 1905), having obtained it in over 90% of cases. The average finding is about 30%.

Morphology

The pneumococcus is a lance-shaped diplococcus, about 1μ in length. It has a definite capsule, which can be demonstrated by special staining methods, such as that of Hiss. It is gram positive, although occasionally gram-negative forms may be seen, and grows on ordinary media, though not very readily. On agar it forms small clear "dew-drop" colonies. If the strain is old and avirulent, the colonies may lose their clear appearance and have a rough surface. On blood-agar the colonies are greenish when viewed by transmitted light, and are surrounded by a small zone of haemolysis.

Most pneumococci are bile-soluble and ferment inulin. This helps to distinguish them from the related streptococci of the viridans group.

The type III pneumococcus differs in its morphology from
the other members of the group. It is sometimes called the Pneumococcus or Diplococcus mucosus. It tends to grow in chains, and forms large sticky colonies, hence its name "mucosus". Because of its chain formation this organism has been called by some workers the Streptococcus mucosus, but its properties of bile-solubility and fermentation of inulin show that it is a true pneumococcus. It is the most virulent of the pneumococci and pneumonias due to it have a high mortality.

Pneumococci produce several potent exotoxins. The most important are (a) a haemolysin (b) a purpura-producing substance (c) a leucocidin and (d) a necrotising substance which causes rapid death when injected into susceptible animals.

The other biochemical activities of the organism are very complex, and will not be dealt with, except for one which may, according to some recent work (Locke et al. 1939), play an important part in the action of M & B 693. This is the fact that the pneumococcus and streptococcus, when growing in the body, form hydrogen peroxide. This substance is lethal to the organism, and they would quickly die out if it were allowed to persist. However, a substance called catalase is produced both by the organisms and the tissues, and this destroys the hydrogen peroxide as it appears. It has been suggested that sulphanilamide and M & B 693 may interfere with this mechanism, in a way which is discussed later (page 71).

The capsule of the pneumococcus is best seen in organisms growing in animal tissues, and soon disappears in culture on artificial media. Friedländer, as I have mentioned before, believed, as far back as 1883 that the capsule was most prominent at the
highest stage of the cell's development. It is now generally accepted that the capsule acts more or less as a protecting envelope for the organism. It contains many complex polysaccharides which are believed to determine the type of the pneumococcus.

In his original paper, it is interesting to note that Whitby (1938) found that when mice infected with pneumococci were treated with M & B 693, the capsules of the organisms swelled up, crenated and disappeared. At the time, he was inclined to ascribe this to a direct action of the drug, which thus stripped the organism of its armour and left it at the mercy of the leucocytes. However, later work (Fleming 1939 a. and b, Stacey and Schluchterer 1939, McLeod 1939), has thrown grave doubts on the importance of capsular damage, and Whitby himself, in a later paper, (McIntosh and Whitby 1939), believes that this phenomenon is not directly related to the action of the drug. The question is more fully discussed later (page 74).

It has been found that among the common laboratory animals, mice and rabbits are peculiarly susceptible to the pneumococcus, especially the first-named, in which death from septicaemia usually results within 24 hours of intraperitoneal inoculation of even a small dose of the organism. From this fact, and its convenient size, it is the animal usually employed in laboratory experiments with pneumococci.

Other Organisms

In view of the results which have been obtained with M & B 693 in pneumococcal pneumonias, it obviously becomes very important to establish whether acute lobar pneumonia may be caused by other organisms, possibly resistant to the action of the drug.
One may go so far as to say that it has become relatively unimportant to decide whether a pneumonia is "lobar" or "broncho" in type, but vitally necessary to decide what is the infecting organism. All of my cases, however, were lobar, so I am only concerned with that type.

The impression gained from a general survey of the literature on the subject is that opinions differ in this country and America. In the latter it is an accepted fact that the Friedländer pneumobacillus, for instance, may in rare cases cause acute lobar pneumonia, while in this country there is a tendency to decry the importance of the organism. It is interesting to see what the leading textbooks in both countries have to say, as representing more or less the accepted opinions held.

In England, Price's Textbook of Medicine (1937) under the heading "Lobar Pneumonia" says that the pneumococcus in this condition may occur alone or may be accompanied by other organisms, such as streptococci, staphylococci or Pfeiffer's bacillus. It is admitted that these organisms and others such as Friedländer's pneumobacillus, B. typhosus and the gonococcus may cause a lobar consolidation, but it says that this should be regarded as a type of secondary pneumonia and differentiated from the acute primary condition under consideration.

It can easily be seen that a lobar consolidation occurring during typhoid fever, or in an acute attack of gonorrhoea may be referred to as a secondary pneumonia, but it is difficult to see why a lobar consolidation due to the Friedländer pneumobacillus or to a staphylococcus or streptococcus without a demonstrable primary focus of these organisms, should be so described. If they are secondary
pneumonias, what is the primary condition? 50% of people ill with tularaemia develop a secondary pneumonia due to the Pasteurella tularensis, but what condition paves the way for a Friedländer pneumonia? Price gives no answer to this question.

In contrast to Price, Taylor's Medicine (1938) says that while in very many cases of acute lobar pneumonia the pneumococcus is the infecting organism, other organisms such as Friedländer's pneumo-bacillus, H. influenzae and Streptococcus pyogenes may rarely cause the condition. The disease known as "Friedländer's pneumonia" is accepted as a clinical entity, with the pneumobacillus as the primary infecting organism. It is described as a severe disease with a bad prognosis, a variable temperature and a marked tendency to suppuration and gangrene in the lung.

In America, Osler's Medicine (1938a) states that Friedländer's pneumobacillus may rarely cause an acute lobar pneumonia. Later (1938 b), he says that the organism may also be found in secondary pneumonias, such as occur in typhoid, typhus or plague, as may the pneumococcus, the streptococcus, staphylococcus and others.

"Friedländer's pneumonia" is accepted as an entity and given a heading of its own (1938b). He says it occurs in the later decades, mainly in men, and has haemoptysis as a leading symptom. The mortality is high and abscess formation is common. It also mentions a rare chronic form of the disease, often mistaken for phthisis.

Cecils Medicine (1937) in discussing whether other organisms than the pneumococcus may cause acute lobar pneumonia, says that while the great majority of cases are caused by this organism, other bacteria may under certain conditions cause a type of acute lobar pneumonia.

It states that notably Friedländer's pneumobacillus produces
a classical type of lobar pneumonia, characterised by a sticky viscid exudate and massive consolidation, usually of several lobes. The mortality is high, and abscess formation common.

It is also suggested that as the haemolytic streptococcus is occasionally isolated in pure culture from the sputum of cases, the natural assumption is that it is the causative organism. It is conceded, however, that the pneumococcus may have been originally present.

From the opinions expressed by these standard works it can be seen that while the subject is controversial, it is in general conceded, especially in America, that Friedländer's pneumobacillus may cause a type of acute lobar pneumonia peculiar to itself, designated "Friedländer's pneumonia." The position of other organisms is more doubtful.

Let me, at this point, confess that for two organisms I hold a brief. These are Friedländer's pneumobacillus and the Staphylococcus aureus. In my short series of cases I encountered one (XII) in which the only organism in the sputum was the Friedländer bacillus and no fewer than four (XIII, XIV, XV and XXI) in which only the Staphylococcus aureus could be found. I propose, therefore, to discuss a little more fully the evidence that these particular organisms can cause an acute lobar pneumonia, first giving a short account of the characteristics of the organism under review.

**Friedländer's Pneumobacillus**

As I have mentioned previously, this organism was discovered by Friedländer in 1882, and was believed by him to be the main cause of acute lobar pneumonia. It is also called Klebsiella pneumoniae, the Bacillus mucosus capsulatus, and various other less-used names. I shall refer to it as Friedländer's pneumobacillus.
Morphology

The organism is pleomorphic, varying in length from 0.6 - 4μ and in thickness from 0.5 - 1.2μ. In other words, it may be seen as a bacillus, or may assume an almost coccoid form, which is its commonest appearance when seen in the body. It was this coccus form that was first seen by Friedländer.

It is gram negative and non-motile, and occurs usually singly or in pairs. Very rarely it appears in short chains.

It has a well-marked capsule which is seen best in organisms recovered from body secretions or in early cultures, just as is the case with the pneumococcus.

The bacillus grows readily on ordinary media, producing large grey or white raised colonies on agar. They have a moist or semifluid appearance, and tend to be confluent. They are very viscid and mucoid. On blood-agar they are surrounded by a wide zone of haemolysis.

Toxin Production

The information as to toxin production is very scanty, the System of Bacteriology (1939) simply stating that no extracellular toxins have been demonstrated. The pathogenic effects of the organism must therefore depend on the action of endotoxins.

Classification

In 1926 Julianelle (1928) found that like the pneumococcus, the organism could be differentiated into several types. He named them A, B and C, and also a remaining untyped group X. They were identified by agglutination and precipitin reactions and by the fact that passive immunity could be developed to individual types in animals by giving specific anti-sera. He found that the distinctions in
type depended on specific capsular polysaccharides, just as are found in the pneumococcus.

Solomon (1937) mentions that Cooper has differentiated the X group into D and E types, and says that there are probably more to come.

The A type is the only one commonly seen in human infections, Solomon (1937) finding it in 95% of his cases and Bullowa and others (1937) in 75% of theirs.

It has been found that some degree of relationship exists between the organism and the pneumococcus. For instance Avery and others (1925) demonstrated chemical and immunological relationships between a strain of Friedländer's pneumobacillus later identified as type B, and a type 2 pneumococcus and Goebel (1927) found a close chemical relationship between the specific capsular polysaccharides of type A pneumobacillus and type 2 pneumococcus, although he did not find any immunological relationship.

Yet another point of resemblance between the pneumobacillus and the pneumococcus is that rough and smooth forms have been found. The smooth strains produce capsules, are type-specific and highly virulent. Mice can be actively immunised against specific types of this form of the organism. The rough strains have no capsules, cannot be typed, and are non-pathogenic.

**Epidemiology**

The organism exists as a commensal in the upper respiratory tract in a small number of normal people. Etienne (1895) found it in and about 4%/Bloomfield (1921) in 5.8%.

Apart from respiratory infections it is found occasionally
in infections of the renal and biliary tract, in cases of septicaemia, otitis media, empyema and pericarditis (Baehr et al. 1933).

The mouse is very susceptible to inoculation with the organism, and is the animal generally used in investigations. It rapidly develops a septicaemia and dies in 8 - 24 hours, when the organism can readily be found in the heart-blood.

Friedländer's Pneumobacillus and Acute Lobar Pneumonia.

When Friedländer was shown to have so over-estimated the part played by this organism in acute lobar pneumonia, there was a strong tendency to travel too far in the opposite direction, and, ascribe to it no importance at all. However, as early as 1886 Weichselbaum (1886) had advanced the view that it did cause a few cases of "croupous" pneumonia, which is indistinguishable from the lobar form.

Since his day evidence has accumulated that a type of acute lobar pneumonia is caused by the Friedländer pneumobacillus, and that it presents features that differentiate it from ordinary pneumococcal pneumonia. Most of the cases have been reported from America, where the bacteriological examination of sputum in pneumonia cases has perhaps been more thoroughly carried out than in this country, at any rate until recent years.

From the time of Weichselbaum there were a few reports of sporadic cases of lobar pneumonia in which the only organism in the sputum was the pneumobacillus, but it would be exhausting and unnecessary to detail them, as in 1915 Sisson and Thompson (1915) reviewed the literature and added four cases of their own. They
found that only thirty-three cases could really be accepted as being primary lobar pneumonias due to the organism, and evolved a picture of the disease which they called "Friedländer pneumonia."

According to them, the condition is invariably fatal. There is an absence of chill at the onset, and toxæmia is profound. The sputum is very typical, being profuse, slimy, non-purulent and very blood-stained.

Since 1915 the condition has been fairly frequently reported, for instance, Cole (1928) reported seven cases of Friedländer pneumonia, of whom five died and two recovered. One of the cases which survived developed a lung abscess, which subsided after surgical drainage.

The largest series in the literature is that reported by Zander (1919). This occurred in association with an influenza epidemic in a German labour camp and consists of 411 cases, more than there is in all the remaining literature, with a mortality of only 35%. Solomon (1937) points out that this series differs from all other reports of the disease in its low mortality, and doubts greatly if the condition was really Friedländer pneumonia. The bacteriological findings were based on the sputum only, without blood cultures, which seems rather an untrustworthy method. Zander believed that the condition was "broncho" rather than "lobar" in nature.

There have recently been two large series of cases published, one by Bullowa and others (1937) and the other by Solomon (1937). This second paper contains an excellent review of the literature on the subject. It seems worth while to deal with these two papers in some detail, as they bring out the present position very well.

Bullowa and others (1937) described 41 cases encountered in 3768 cases of acute lobar pneumonia seen at the Harlem Hospital, giving
an incidence of 1.1%. This does not differ greatly from the figure of 0.4% given by Cecil (1927).

Bullowa takes it as an accepted fact that Friedländer's pneumobacillus can cause an acute lobar pneumonia and also mentions the chronic form of the disease, which simulates phthisis. In his cases the diagnosis was based on the isolation of the bacillus from the sputum, confirmed by finding it on lung suction, in the blood, or both. The usual X-ray finding was a massive lobar consolidation, which looked almost like fluid.

He typed the organisms in most of his cases and found type A in 24, B in 2, C in 1 and the X group in 8. The other 6 cases were not typed, only A serum being used.

Twenty-one of his cases had an onset like a typical lobar pneumonia with chill and the classical signs of consolidation. Occasionally there were no physical signs present.

In two thirds of the cases the sputum was merely rusty. In the other one third it was thick, gelatinous and diffusely bloody, as described by Sisson and Thompson. One third of the cases had a leucopenia. The temperature was variable.

The mortality was very high, 83% of the series dying. 66% had positive blood cultures and of these 93% died. Death was rapid, usually occurring about 5 days from the onset.

He gave type A antiserum to 6 cases, of which 3 died, and suggests that it may be a useful line of treatment. The value of this conclusion is lessened by the fact that only 1 of his 6 cases had a positive blood culture and it died. Of the 13 cases of type A infection treated without serum 10 had organisms in their blood.
Solomon's series of cases consists of 32 which he encountered in the course of 5000 cases of acute pneumonia. Five of these he considers may have been "broncho" rather than "lobar" pneumonias, but the other 27 were definitely lobar. The average age of his cases was 49 years, and he suggests that the disease is commonest in late middle age. There were 26 men in the series, and only 4 women.

The disease usually began with an abrupt onset with chill and pleuritic pain. Toxaemia was profound.

The temperature was often not very high, in 50% of his cases never going above 100°F. A curious finding was that herpes was rare.

The physical signs were often not those of frank consolidation, and he suggests that the sticky exudate produced may block the bronchial tubes.

He lays great stress on the appearance of the sputum which he says is in many cases pathognomonic. It is usually a thick mixture of blood and mucous, brick red in colour, looking like a uniform emulsion.

He found a marked tendency to leucopenia, 11 cases having an absolute leucopenia and 4 a relative one.

The clinical course was generally fulminating; 31 cases died, giving a mortality of 97%, a startling figure for any disease.

The organism present was typed in ten cases and was found to be A in every one. In no case did he find a secondary infection with another organism.

Blood-cultures were taken in 27 cases, and 19 were positive. Only 1, however, of the 8 cases with negative blood cultures survived
He concludes that bacteraemia has little to do with the prognosis. This is not supported by Bullowa's experience.

Many cases developed septic complications before death. Six developed gross lung necrosis with cavitation. Two cases developed empyema, with a pure culture of the bacillus. Six cases developed pleural effusion and 3 meningitis, the organism being found in the cerebro-spinal fluid in all of them.

In 5 cases due to the type A pneumobacillus he tried giving specific antiserum. All of the cases died. He admits that only in 2 cases, however, were sufficient doses given, and therefore little stress can be placed on the results.

The single case which recovered had a right upper lobe consolidation. Blood-culture was positive on only one occasion. He had a crisis on the tenth day of his illness, and recovered without any special treatment.

Perhaps the strongest criticism of the role played by Friedländer's pneumobacillus in acute pneumonia came from Baehr and others (1933). They considered that in respiratory infections the organism was purely a secondary invader, and that it was concerned chiefly with infections of the biliary system, genito-urinary system and perforations of the intestinal tract.

In pneumonia they believed that if the bacillus was not a secondary invader, it reached the lung from the gall-bladder, kidney or intestinal tract, either directly or via the blood.

They conclude that the views of those who give the organism a primary part in the causation of acute lobar pneumonia are due to the fact that bacterial observations have only been made post-mortem, and point out that pre-agonal and post-mortem invasion
of the blood by this organism is common in any condition.

Solomon (1937) very strongly opposes this view in his paper. He first of all points out that if Friedländer pneumonia is a metastatic infection, one would expect invasion of the blood before localisation in the lungs. In 7 of his cases the organism was found in the sputum from 1 to 8 days before it was found in the blood. In 4 of these cases it was also found on lung-puncture. In 6 other cases the bacillus was found in the lungs or sputum or both, while the blood was sterile throughout the illness.

He also adds that in only 4 of his cases were biliary, genito-urinary or gastro intestinal lesions found, which makes the origin of infection in these situations very unlikely.

Also, in the great majority of his cases the blood infection was maximal at the height of the illness, and not just before death. The bacillus was isolated in nearly every case shortly after admission, at an early stage in the disease.

As far as he could find, in his series, the Friedländer pneumobacillus never invaded a lung already infected by another organism. In only 2 cases were any other organisms present at any stage, and these he considered to be mouth contaminants.

From a survey of the literature, of which examples have been given, the only conclusion that can be reached is that, in a small percentage of acute lobar pneumonias, the Friedländer pneumobacillus is the causative organism. Also when the organism is primary, a special type of lobar pneumonia with a very high mortality, is produced. The characteristics of this pneumonia appear to be those of an intense toxaemia with blood-stained sputum, leucopenia and rapid and almost invariable death. In cases which survive long
enough, septic complications such as lung abscess and empyema are common. The diagnosis is made by the finding of the causative organism in the sputum, either alone or in marked predomination, and is confirmed by finding it also on lung-puncture or suction, or in the blood.
Staphylococcus aureus.

This organism is much commoner and better known than the Friedlander pneumobacillus, so only a short review of its principle characteristics will be given.

Morphology.

The organism is a small Gram-positive spherical coccus, about 0.7 - 0.9 μm in diameter. It grows in groups being usually seen in characteristic grape-like masses. It proliferates freely on all ordinary media, forming fairly large round colonies, usually about 3 - 4 millimetres across. The colour of these colonies is usually yellow, hence the name "aureus", but rarely they may be very pale yellow or white, causing confusion with other types of staphylococci.

On blood-agar the colonies are usually surrounded by a definite zone of haemolysis. This, however, is not invariable, as occasionally definitely virulent staphylococci fail to produce this phenomenon.

Sugar Fermentation.

Staphylococcus aureus almost always ferments mannitol, and this is the only sugar reaction which will be mentioned. This has been used to distinguish the organism from non-virulent albus type staphylococci, but is also unfortunately not invariable, although Julianelle (1937) believes it is accurate to within 5%.

Toxin Production.

Endo and exo-toxins are produced. The exotoxins are as follows:

(1) Two haemolysins \( \alpha \) and \( \beta \)
(2) A leucocidin.
(3) Skin-reacting toxin.
(4) A necrotoxin. This causes rapid death when injected into animals.

(5) Coagulase. This causes clotting of plasma, human and animal.

The only one to which I intend to refer is the last, as it is the basis for the now generally accepted "coagulase test" for the determination of the virulence or otherwise of any individual staphylococcus. In blood-culture work this is often very important as the commonest contaminant is an avirulent type of staphylococcus, which inhabits the skin.

Cruickshank (1937) was the first to apply this property of the staphylococcus, which had long been known. He found that only the virulent Staphylococcus aureus and its white variants, produced this coagulase, which he found was an enzymic substance, acting in a manner similar to thrombin. Other staphylococci, Streptococcus pyogenes, viridans and faecalis, pneumococci of types I, II and III and E. diptheriae, (cornebacterium diptheriae) gravis, mitis and intermediate, all failed to produce the substance. He found that the property did not disappear with age or frequent subculture.

The presence of coagulase is easily demonstrated by inoculating staphylococci of a virulent strain, into any animal plasma, when clotting occurs on incubation. Cruickshank proposed that this phenomenon should be accepted as a test for virulence for staphylococci, and as such it is now accepted.

Types of Staphylococci.

There is only one "type" of Staphylococcus aureus, but many strains of varying virulence, exist. However, as I have mentioned above, other staphylococci, quite distinctly separated
from the aureus group exist. These are relatively non-pathogenic and fall into two large classes.

(a) Staphylococcus citreus, producing pale yellow colonies on agar.

(b) Staphylococcus albus, producing white colonies. This last is commonly found in the skin.

Both organisms must be carefully differentiated from Staphylococcus aureus, which can easily be done by the coagulase test mentioned above.

Epidemiology of Staphylococcus aureus.

The organism may cause a large number of common conditions, being perhaps the most commonly found bacterium in human infections. Pustules in the skin, boils, carbuncles, septicaemia and pyaemia and many other conditions may be caused by it. There is always a marked tendency to the formation of localised abscesses in staphylococcal infection which is very fortunate in view of the very high incidence of infection. This tendency may be connected with the production of coagulase, which closes blood and lymph channels leading from the point of invasion.

The coccus is found in abscesses of all types and situations, in meningitis, empyema and a host of other conditions, too numerous to detail. I shall, try to show that it may also be found as the primary cause in some cases of acute lobar pneumonia.

The organism is fairly commonly found in the throats of apparently healthy people, especially in children. Wheeler and others (1935) having found it in the throats of 70% of children in November and December, when bodily resistance is lowest. It is therefore possible that an autogenous infection may occur as with the pneumococcus, from a lowering of bodily vitality, an elevation in virulence, or a combination of both.
Staphylococcus aureus and Acute Lobar Pneumonia.

While it would seem that it must now be accepted that the pneumobacillus of Friedländer can cause an acute lobar pneumonia, the position of the Staphylococcus aureus is much more controversial. There is, however, some evidence that, in rare cases, it may cause the condition.

It is generally admitted that the organism is commonly found in bronchopneumonia, usually associated with other organisms, but occasionally alone. Chickering and Park in 1919 described 153 cases of broncho-pneumonia following influenza in which only the Staphylococcus aureus was found. All of the cases described were fatal, and the organism was found on post-mortem blood-culture. Since then other workers, for example Cole (1928), have found the organism to be primary in a few cases of acute broncho-pneumonia, and Cecil's Medicine (1937 b) gives the condition a heading of its own, calling it "Staphylococcus aureus Pneumonia", and mentioning that it is a very fatal form of broncho-pneumonia, often associated with influenza. It is only fair to note that this article is written by Chickering, quoted above.

The occurrence of acute lobar pneumonia due to the Staphylococcus aureus is a much more questionable matter, and it is difficult to find cases in the literature, because clinicians, in America particularly, have largely ceased to talk of acute "lobar" or acute "broncho" pneumonia, and merely refer to "acute pneumonia".

I have already advanced the view that the exact pathology of "acute pneumonia" is a secondary matter compared with the bacteriology of the condition, because we now have the means to attack specific organisms. However, all of my staphylococcal cases,
which I shall discuss later, were "lobar" in nature, so I wish to see what reports there are of a similar condition.

The bacteriological reports of large series of cases do suggest that such a condition exists, though ordinarily very rarely. Cecil, (1927), in a series of 2000 acute lobar pneumonias, found the staphylococcus alone in 0.1%. Habbe (1929) found it 4 times in 131 cases, an incidence of 3%. Cole (1932) found it in 1.8% of 1383 cases, and Bullowa (1938) in 0.7% of 3065.

Several sporadic cases have been described and I have found two short series in the literature.

To begin with the sporadic cases, Wallace (1937) describes the case of a child 4 weeks old admitted 2 days after the onset of a pneumonia. She died 30 hours after admission. A post-mortem examination was done and consolidation and cavitation were found, limited to the left lower lobe. The other lung showed only bronchitis and emphysema. There was also an inspissated empyema on the left side.

The only organism which was found, both in the empyema and the lung, was the Staphylococcus aureus.

Cohen (1938) reports 3 cases of primary staphylococcal pneumonia, of which the first at least seems to have been lobar in nature. This was the case of a boy aged 12 years whose illness began abruptly with a rigor and rapid rise of temperature. The clinical signs and X-ray appearances at first suggested a lobar consolidation, limited to the right lower lobe. A bronchopneumonia later developed in the left lung. It seems probable that this was due to bronchogenic auto-infection of this lung, by the sputum which he was bringing up from the lobar condition in his other lung. He recovered in 4 weeks without any special treatment.
The other two cases were both babies with empyemata. The pneumatic condition seemed to be limited to one lung in both cases, suggesting a lobar type of infection, but the presence of empyemata made this difficult to determine. One case died. The other recovered without special treatment.

The two series of cases I referred to, are those of Reimann (1933) and Agnes Macgregor (1936).

Reimann describes 6 cases, 2 of which were fatal, in which he thinks that the Staphylococcus aureus was the primary infecting organism. He is not concerned with whether the pneumonia was "broncho" or "lobar", but from a study of his case summaries, 5 of the cases seem to have been lobar.

All of his cases developed lung abscesses, and he suggests that staphylococcal pneumonia is an entity characterised by the following:

(1) The presence of staphylococci in the lung.
(2) The presence of staphylococci in the sputum.
(3) Remittent fever.
(4) Marked sweating.
(5) Abscess formation.
(6) A high mortality, although 4 of his 6 cases recovered.

It is only fair to note that in the discussion which followed the presentation of Reimann's paper Dr. Sutcliffe of Boston challenged the view that the staphylococcus can cause a primary pneumonia. He said that in examining the sputum of 1067 cases of "acute pneumonia", (he does not differentiate "lobar" and "broncho") he found the Staphylococcus aureus in 9% of cases, but always in association with other organisms.
As an example, he quotes a very interesting case of an acute lobar pneumonia which had both a type I pneumococcus and a Staphylococcus aureus in the sputum. Type-specific serum cured the pneumococcal infection, but the staphylococcus persisted and killed the patient. At a subsequent post-mortem, a pure culture of Staphylococcus aureus was found in the lung.

His view was that staphylococcal pneumonia is purely a secondary condition, the pneumococcus usually being the primary invader, but he pointed out that such a secondary infection was, in his opinion, a complication which might interfere with specific serum therapy.

From my point of view the most interesting series of cases is that of Agnes Macgregor, (1936), as they occurred in Edinburgh in 1935 and 1936, while I encountered my cases in the same city in 1939.

She describes 10 fatal cases of acute pneumonia in children, in which the staphylococcus was found either alone or predominating in the lungs post-mortem. In 9 cases the staphylococcus was an aureus, and in the remaining one an albus. She does not mention any virulence tests done on this last organism, and it seems probable that it may have been a white variant of an aureus, in view of the usual non-pathogenicity of the Staphylococcus albus.

At post-mortem the consolidation in 9 of the cases was definitely lobar, and in only 1 case lobular. One of the lobar cases had 2 lobes affected. Only 1 lobar case had a concurrent bronchitis.

Four cases had consolidation with commencing pus-formation. The remaining 6 had definite lung abscesses and empyemata.

In 4 of the cases a mixed infection was present, with the
staphylococcus predominating. In the other 6 only the staphylococcus could be found. She regards these last as examples of true primary staphylococcal pneumonia, and the others as secondary infections by the staphylococcus.

One case, in which Staphylococcus aureus alone was found in the lung, and a type 2 pneumococcus in the blood, is interesting in the light of a rather similar combined infection that I encountered. Macgregor's case died 8 hours after the onset of the pneumonia, and she notes that this combination of organisms seems very fatal.

She suggests that the Staphylococcus aureus can cause a primary lobar pneumonia, which is characterised by an early tendency to pus-formation, which later goes on to lung-abscess and empyema. Because of this, the mortality is very high.

She notes that she had never encountered a series of cases like this before. All of them occurred within 9 months. She suggests that during that period there may have been an increase in the virulence of the staphylococcus in Edinburgh. This is again an interesting comparison with my experience.

The most serious criticism of this series of cases seems that all of the bacteriological investigations were done post-mortem. It is unfortunate that these findings could not be correlated with examinations made of the sputum during life. However, as 6 cases showed only the Staphylococcus aureus, it would seem that this must have been the infecting organism. The presence of this organism in a mixed infection of the lungs post-mortem would seem of little significance, but a pure culture does suggest that it must have been the infecting organism during life.
From the evidence which I have reviewed, I think I may say that there is at least a certain amount of proof that the Staphylococcus aureus may cause an acute lobar pneumonia. In a later section, (page 125), I shall discuss the part played by this organism in my cases.
Symptomatology of Acute Lobar Pneumonia.

The symptomatology of acute lobar pneumonia is so well-known that it seems unnecessary to describe it in detail here. The sudden malaise, with a rigor, rapid rise of temperature, stabbing pain in the side and rusty sputum, is one of the most typical and easily recognised clinical pictures in medicine.

I have already discussed the variations from this which are found when certain unusual organisms such as the Friedlander pneumobacillus and Staphylococcus aureus are present instead of the usual pneumococcus. (pages 18 & 28).

I shall therefore proceed to a discussion of certain aspects of the pathology.

Pathology of Acute Lobar Pneumonia.

Path of Infection.

It used to be held that organisms normally present in the throat and mouth invaded the blood stream in conditions of lowered bodily resistance, and then localised in the lung.

Grave doubts were cast on this conception in 1920 when Cecil and Blake (1920) experimenting with monkeys, came to the conclusion that acute lobar pneumonia is caused by the invasion of the normally sterile bronchi by organisms from the mouth, and that the process begins in the hilum and spreads centrifugally. They believed that invasion of the blood-stream was a secondary event, which might, or might not, take place.

Although the question is still controversial, this view of the sequence of events is now accepted by most authorities.

Invasion of the Blood.

As I have just said, this is now generally accepted to be
a secondary event. Its incidence in different series is very variable, probably depending, apart from the question of the virulence of the infecting organism, on such matters as the time taken to examine the blood after withdrawal, and the nature and quantity of the culture medium used.

However, the average figure given in the standard textbooks is about 30%. The incidence is highest when type 3 pneumococcus is the infecting organism and lowest when group IV is present. Types I and 2 are intermediate, the incidence being higher with the latter.

A positive blood culture usually indicates a severe infection, and its persistence in spite of treatment, means that the prognosis is very grave.

Changes in the Lungs.

The changes in the lungs in acute lobar pneumonia when the pneumococcus is the infecting organism are very well known, and I do not propose to describe them in detail. The process is classically divided into 4 stages, all of which may or may not be seen. They are as follows:

(a) Stage of engorgement.
(b) Stage of red hepatisation.
(c) Stage of grey hepatisation.
(d) Stage of resolution.

When the infecting organism is not a pneumococcus, the changes in the lung may differ from those seen in the typical disease, for instance, when the pneumobacillus of Friedländer is the infecting agent the exudate in the lungs is very sticky and mucoid, similar to that seen when the type 3 pneumococcus
is present. (Muir, 1936, McCallum, 1936). There is also a very marked tendency to necrosis of the lung-tissue with abscess formation, and also to the development of empyema. (Solomon, 1937, Bullowa 1937).

When the Staphylococcus aureus is the infecting organism, this tendency to lung-necrosis is even more marked, large cavities usually being found in the affected lobe or lobes. (Macgregor, 1936, Reimann, 1936, Cecil, 1937). Emphyema also seems to occur commonly when this organism is present, especially in children. (Cohen, 1936, Wallace, 1937).

With both of these organisms, naturally, resolution in non-fatal cases tends to be slow, and results in a large amount of fibrosis.

Incidence of Complications.

When trying to assess the value of a new drug, it is always interesting to try to discover its value in preventing the usual complications of the disease under treatment. I therefore now propose to insert the average frequency of the main complications of acute lobar pneumonia in cases treated without M & B 693. I shall later use these figures for comparison with treated cases.

Emphyema.

This is the most serious of the common complications of acute lobar pneumonia, both from the risk to the life of the patient, and the long and wearisome convalescence it entails if he survives.

Pye-Smith and Beddard (1909) found empyema in 3.7% of 7,868 cases. Howard found it in 3% on combining the statistics of almost 25,000.

Although the pneumococcus is usually found alone in the
pus, streptococci and other organisms may quite frequently be present. Occasionally these other organisms are found alone.

**Simple Effusion.**

This is quite a common complication, as would be expected, since a dry pleurisy is an essential part of the disease, but it usually goes unrecognised, and merely indicates a mechanical irritation of the pleural surfaces.

Extensive pleural effusion was found in only 1.6% of Pye-Smith and Beddard's cases.

Occasionally these effusions contain a few pneumococci, and they may then go on to empyema.

**Delayed Resolution.**

This occurs in a small and variable proportion of cases, the signs of consolidation persisting for weeks, instead of days. According to Cecil (1937 c), the average incidence is 3 to 4%.

**Lung Abscess.**

This is a rare complication in pneumococcal pneumonias, usually occurring in less than 0.5% of cases. (Lord, 1915, Musser and Norris, 1907).

I have already mentioned that it is much commoner in pneumonias due to the pneumobacillus of Friedländer or the Staphylococcus aureus.

**Acute Otitis Media.**

This is a rare complication in adults, practically only being seen in children.

**Pericarditis.**

This is seen in 3 to 7% of cases, and is a very serious complication when it does arise, frequently being a terminal event.
Other complications, such as endocarditis and meningitis, are so rare that they are not often seen in practice. Meningitis, for instance, occurs in only 0.01% of cases, according to Howard.
III. The Sulphonamides and their Action.

Development of the Sulphonamides.

Although the introduction of the sulphonamide group of drugs to therapeutics may be said to date from the paper published by Domagk in 1935, (Domagk 1935), on the use of Prontosil in experimental and clinical streptococcal infections, the actual discovery of the group of drugs goes back to before the war. Several times their life-saving properties were almost stumbled upon, but always they were missed.

The first man to light upon one of this group was Gelmo, in 1908. He was a chemist, working for the dye industry, and one day prepared a compound para amino benzene sulphonamide, which is the drug now known to the world as sulphanilamide. The essential part of its formula, which is given below, is a sulphonamide group attached to a benzene ring in the para position:

\[
\begin{align*}
\text{H}_2 \text{NO}_2 \text{S} & \quad \text{NH}_2 \\
\end{align*}
\]

Unfortunately Gelmo's interest in the compound was purely scientific, and its great potentialities went unrecognised.

In the next year the first azo dyes were prepared with sulphonamide and substituted sulphonamide groups. (Hoerlein, et. al. 1909). These were successfully used for textile purposes.

The idea of investigating these azo compounds from a medical standpoint occurred to Eisenberg in 1913. He found that many of them had a bactericidal action in vitro, and decided to investigate the action of chrysoidine (diaminoazobenzene) in vivo. Unfortunately, he found that this substance was without therapeutic effect in animals, and abandoned his investigations.
He was followed in 1914 by Tchichibabin and Zeide (1914), who, using chrysoidine as a basis, synthesised pyridium (benzene azo alpha alpha diamino pyridine). This has been used as a urinary antiseptic since 1926, but its powers are very suspect. Scarlet red (toluyl azo toluyl azo betanaphthol) was in the same year, shown to have the power of stimulating the growth of epithelial cells.

1919 saw the closest approach as yet to the discovery of the tremendous latent possibilities of the sulphonamides. Jacobs and Heidelberger decided in that year to investigate the possibility of increasing the therapeutic power of the quinine molecule by linking it with diazo compounds. They used dihydro cuprein and, among other compounds, linked it with sulphanilamide.

They, like Eisenberg, found that many of their compounds were highly bactericidal in vitro, and mentioned that Wollstein, their co-worker, would shortly investigate their bacteriological value, but this, unfortunately, she never did. It is perhaps as well that subsequent investigation (Buttle et al. 1936, 1937) has shown that the substance formed by the combination of dihydrocuprein and sulphanilamide does not possess antistreptococcal powers to a therapeutic degree.

No new compounds of real clinical value were discovered until 1932, when the chemists Mietzsch and Klarer patented a new azo dye, again for the industry. This drug was none other than prontosil, also known as prontosil rubrum, prontosil flavum and sulphonamido-chrysoidine. It will be referred to as "prontosil". It is 4-sulphamido-2:4-diaminoazobenzene, and is a red powder, which is 0.25 per cent. soluble in cold water forming a yellowish solution.
Its formula follows.

\[
\text{Prontosil} \quad \begin{array}{c}
\text{H}_2 \text{NO}_2 \text{S} \quad \text{NH}_2 \\
\text{N} = \text{N} \\
\text{SO}_3 \text{Na}
\end{array}
\]

This time, fortunately, the clinical potentialities of the drug were discovered, by Domagk, the director of the experimental pathological laboratory at Elberfeld. He found that it had remarkable powers of preventing and curing streptococcal septicaemia in mice. (Domagk 1935).

During the same year Mietzsch and Klarer discovered a new drug with similar properties, which was however, much more soluble. This was prontosil soluble, also called prontosil S, prontosil 2, Streptozon or Neoprontosil. Hereafter it is called "prontosil soluble". It is the disodium salt of 4-sulphonamido benzene-2-azo-7-acetylamino-1-hydroxynaphthalene-3:6-disulphonic acid. It is 4 per cent soluble in cold water, and freely soluble in hot, remaining in solution as long as the temperature is kept above 37°C. It forms a red solution. Its structural formula is given below.

\[
\begin{array}{c}
\text{H}_2 \text{NO}_2 \text{S} \quad \text{OH} \\
\text{N} = \text{N} \quad \text{NHCO CH}_3 \\
\text{Na O}_3 \text{S} \quad \text{SO}_3 \text{Na}
\end{array}
\]

As can be seen, its formula is remarkably different from that of prontosil. All they have in common is half of each molecule, consisting of the sulphonamide group attached to the azo group in the para position by a benzene ring. The only explanation for their remarkable similarity of action in the body is that the essential factor for their action is the sulphonamide group in the para position. To support this, it was found that compounds with the
sulphonamide group in any other position were quite devoid of antistreptococcal action. (Mietzsch and Klarer 1932-1934).

There is no question but that the credit of realising the therapeutic possibilities of azo compounds with a sulphonamide group in the para position belongs to Domagk. He embarked on a very careful investigation of the effects of prontosil in the treatment of experimental streptococcal infections in mice, and published his results in 1935. (Domagk 1935). Following this article, many publications, too numerous to be given in detail, appeared in the German and other literature supporting by clinical findings his experiments.

Research into the action of these compounds was actively stimulated in France, and in 1935 Girard prepared what he called sulphonamido-chrysoidine, according to the directions given in the Mietzsch and Klarer patent. (Mietzsch and Klarer 1932-1934). This he called rubiazol I, but it is usually taken to be identical with the German prontosil. He also prepared a similar compound, carboxyl sulphonamido chrysoidine, known as rubiazol IV.

These drugs and prontosil and prontosil soluble were investigated and their action compared by Levaditi and Vaisman, at the Pasteur Institute. (Levaditi and Vaisman 1935-1936). They confirmed the work of Domagk on their action on streptococci and concluded that rubiazol I and prontosil were equal in effect with rubiazol IV, but that prontosil soluble was not so efficacious.

Meanwhile, however, other French workers began to try to find a simpler compound outside the azo series, which would have effects similar to prontosil. Similar independent research was going on in Elberfeld. The Tréfouels, Mitti and Bovet (1935, 1936),
postulated that in the tissues prontosil was broken down to triaminobenzene and sulphanilamide, which they assumed to be the active part of the molecule. They therefore synthesised para amino benzene sulphonamide or sulphanilamide. It is also known as prontosil album, sulphonamide-P, colsulamyde, P.A.B.S., prontylin, streptocide sulfamidyl and by many other names. It will be referred to as sulphanilamide. Its formula is below.

\[
\begin{align*}
H_2O_2S & \quad \text{Sulphanilamide} \\
& \quad \text{NH}_2
\end{align*}
\]

They found that this compound was just as active against the Streptococcus as the original prontosil, thus proving that the azo-linkage was not essential.

They also synthesised para acetyl amino benzene sulphonamide which they claimed was a breakdown product in vivo, and had a feeble bacteriostatic action against the streptococcus. During 1936 and 1937 they synthesised many derivatives of sulphanilamide, but were unable to find any with a superior action against the streptococcus (Trefouels, Nitti and Bovet 1936, 1937).

In England Colebrook and Kenny (1936) made a very carefully controlled investigation into the action of prontosil in puerperal sepsis and amply confirmed the claims made by Domagk as to its anti-streptococcal action. (Colebrook and Kenny 1936, Colebrook, Buttle and O’Meara 1936.)

In addition many compounds related to sulphanilamide were being tested in streptococcal infections in mice, and it was found that compounds containing a sulphone group were effective, especially para para dinitro diphenyl sulphone and para para diamino diphenyl sulphone. (Buttle, Stephenson, Smith, Dewing and Foster 1937).
Whitby (1937) tested out two other related compounds on streptococcal infections in mice. These were para-benzyl-amino benzene-sulphonamide, known as Proseptasine and disodium para (γ phenyl-propyl-amino) benzene sulphonamide γ γ disulphonate, this being the soluble product known as Soluseptasine. Proseptasine had been first synthesised in France in 1936 (Goissedet, Despois, Gailliot and Mayer.) He found these compounds just as efficacious as the original prontosil and prontosil soluble.

Their formulae follows:

\[
\begin{align*}
\text{Proseptasine} & : H_2NO_2S \quad \text{H}_2\text{C} \\
\text{Soluseptasine} & : H_2NO_2S \quad \text{HN} = \text{CH} - \text{CH}_2 \quad \text{HN} - \text{CH} - \text{CH}_2 \\
& \quad \alpha \beta \gamma \\
& \quad \text{SO}_3\text{Na} \quad \text{SO}_3\text{Na}
\end{align*}
\]

In France in June 1937 dinitro-diphenyl-sulphide and dinitro-diphenyl-disulphide were found to be active, (Fourneau et al. 1937) and later in the year it was found that sulphoxides were very efficacious against experimental streptococcal and gonococcal infections (Girard et al. 1937).

While all this research was proceeding abroad, Elberfeld, the home of prontosil, was not inactive. Domagk, Klarer and Metzsch continued their investigation, with a view to finding drugs which would have an equal action to sulphanilamide on streptococci and yet have a much more powerful action than that drug on other organisms.

During 1936 and 1937 three compounds known as diseptal A B and C were tested and the results were published in October 1937.
It was stated that they were as powerful as sulphanilamide against streptococcal infections in mice, while all three showed a striking increase in potency against staphylocoecal infections especially diseptal A, which was named "Uloron". They were also more active against gas-gangrene infections. A and B being equal and being much stronger than C. (Domagk 1937.)

Their formulae follow:

\[(\text{CH}_3)_2\text{NO}_2\text{S} - \bigcirc - \text{HNO}_2\text{S} - \bigcirc - \text{NH}_2\]

Diseptal A

\[\text{CH}_3\text{HNO}_2\text{S} - \bigcirc - \text{HNO}_2\text{S} - \bigcirc - \text{NH}_2\]

Diseptal B

\[\text{H}_2\text{NO}_2\text{S} - \bigcirc - \text{HNO}_2\text{S} - \bigcirc - \text{NH}_2\]

Diseptal C

All, as can be seen, are similar compounds, differing only in the substitution attached to the final sulphonamide group.

Later in the year, it was claimed that these compounds were more effective than sulphanilamide against the gonococcus. (Grutz 1937 and Felke 1937.)

Research had also been directed in various parts of the world towards finding a drug more potent than sulphanilamide against the pneumococcus. Domagk during 1935 and 1936 (Domagk 1935, 1936) had tried out the original prontosil and also sulphanilamide on pneumococci. He found that both had some effect on type III pneumococci, but none on types I and II. He found sulphanilamide more effective than prontosil.
Many other workers during 1936 and 1937 had similar results, and sulphanilamide was shown to be of very little value against the pneumococcus. Buttle in 1937 emphasised that the drug merely delayed death in mice infected with pneumococci, Whitby in the same year found almost no protection against 10,000 lethal doses of type I pneumococci, using intraperitoneal inoculation, in mice, (Buttle 1937, Whitby 1937), and in December 1937, Douthwaite summed up the position by saying that it was doubtful if sulphanilamide had any action against the pneumococcus, (Douthwaite 1937.)

Other compounds investigated had been the benzylidene base of dianmodiphensulphone (Buttle 1937), which was found to be more effective against pneumococci than sulphanilamide, but was also four times more toxic, and two diamino-benzene-sulphonanilide compounds (Whitby 1937) which were three times more effective.

In 1937 a compound, 2 (para-amino-benzene-sulphonamide) pyridine was produced by Ewins and Phillips in the laboratories of May & Baker Limited.

Its formula is given below:

\[
\text{NH} - O_2S\text{NH}_2 \quad \text{M&B 693}
\]

2- (para-aminobenzene sulphonamide) pyridine

The makers suggested that for the chemical name of the drug 2-sulphanilyl-amino-pyridine should be used. They explain that while the first name is scientifically accurate, it does not seem
sufficiently descriptive for non-chemists. They prefer the second name, which emphasizes the relation of the compound to sulphanilic acid and aminopyridine, and write the structural formula as follows:

\[
\begin{array}{c}
\text{SO}_2 \\
\text{NH}_2
\end{array} - \begin{array}{c}
\text{NH} \\
\text{N}
\end{array}
\]

2-sulphanilyl-aminopyridine. M & B 693.

As I have said, the drug is variously known as M & B 693, sulphapyridine, sulfapyridine and Dagenan, and will be referred to as M & B 693.

From the first structural formula given, it can be seen that the compound differs from sulphanilamide by having one hydrogen atom of the sulphonamide group replaced by a basic pyridine group. One of its most important physical properties is its lack of solubility. At ordinary temperatures it dissolves in water only to the extent of 1 in 3000.

The substance was investigated by Whitby (1938), using the method of mouse-inoculation. His conclusions were as follows.

(a) M & B 693 is active against pneumococci of types 1, 2, 3, 5, 7 and 8, and especially so against types 1, 7 and 8.

(b) It causes disintegration of the capsule of the pneumococcus.

(c) It is as active as sulphanilamide against the haemolytic streptococcus and the meningococcus.

(d) It has a low toxicity for animals, and does not produce porphyrinuria in those tested (Wien 1938).
The drug was first clinically investigated by Evans and Gaisford (1938), who found that it was very effective against pneumonia in the human subject, their mortality in 100 cases treated with the drug being 8%, compared with 27% in 100 controls.

Since then many other clinical investigations have established the drug as an extremely successful chemotherapeutic agent against the pneumococcus.

Absorption and Excretion of the Sulphonamides

The two earliest preparations, prontosil and prontosil soluble, are absorbed very rapidly. Prontosil appears in the urine one hour after it has been given by mouth, and prontosil soluble ten minutes after subcutaneous injection.

In the body both drugs are partly broken down to sulphanilamide, which is excreted partly free and partly in an acetylated form. (Fuller 1937.)

Prontosil

Prontosil, unlike most of the other drugs in its class, is only excreted slowly. Colebrook and Kenney (1936) found that given by injection, it still protected mice against streptococci 4 days later. This is in contrast to the short lived action of prontosil soluble and sulphanilamide. This was confirmed by Fuller (1937) who found that only a small fraction of injected prontosil was excreted by a mouse in five days.

Prontosil Soluble

Prontosil Soluble is excreted very rapidly. Fuller (1937) found that the whole of a moderate dose of prontosil soluble injected into a mouse was excreted within six hours. Rosenthal
and others (1937) recovered 95% of the drug from rabbit urine 5 hours.

**Sulphanilamide**

Sulphanilamide is also absorbed very rapidly. Marshall et al. (1937) have shown that a dose given by mouth is completely absorbed in four hours. The drug is rapidly excreted in the urine, partly unchanged and partly as the acetyl compound para-acetyl-aminobenzene-sulphonamide. The amount of the drug which is excreted in the acetylated form seems to be variable. Marshall et al. (1937) and Hoerlein (1937) state that a large proportion is acetylated, while Johnson (1938) says that most of the sulphanilamide is excreted unchanged. It has been shown that sulphanilamide is partly converted into the acetylated form in the liver. (Harris and Klein 1938). Hansen (1939) says that about 20% of the drug is usually present in the blood as the inactive acetylated form, but that it may be as high as 40%. He believes that the extent of this percentage is not correlated with the therapeutic results obtained.

Marshall et al. (1937) also state that the blood concentration after oral administration is maximal after three hours, and falls slowly to zero in about 24 hours. They find that the drug is absorbed wholly from the small intestine and not at all from the stomach. It is very diffusible and rapidly finds its way into all the organs and tissues of the body. Hansen (1939) mentions that it is selectively absorbed on to the red corpuscles of the blood, the concentration there being 50% greater than in the plasma.

According to later work by Marshall (1939) 90% of the
drug can be recovered from the urine either as sulphanilamide or as the acetylated form, so it is not retained in the body.

From these findings it is obvious that the drug must be given frequently, if it is desired to keep a constant concentration in the blood. It is found in practice that this can be done by giving 1 gramme of the drug four-hourly. Long and Bliss (1937a. and c), state that for the treatment of a severe infection a blood-concentration of 10 mg. % is necessary, and that this can be obtained by a dosage scale of 1 gramme per day to 20 lb. of body weight. This approximates to a dosage of 1.5 gramme 4 hourly to an adult man.

M & B 693

M & B 693, according to Long and Feinstone (1938), is absorbed more slowly than sulphanilamide, the blood concentration not reaching its peak until about 4 hours after a dose has been given by mouth. There is a definite variability in the rate of absorption, not only in different people, but in the same person at different times. As compared to sulphanilamide, relatively more of the drug in the blood is acetylated and therefore inactive. It is less diffusible than sulphanilamide.

Long and Feinstone (1938) have also found that the excretion of the drug is much slower and less complete than is that of sulphanilamide. While the drug is being given 6-hourly, 50 - 65% of the amount given is excreted in the urine in a 3 day period. This is a much lower percentage than that found with sulphanilamide. They suggest that a considerable amount of the drug given by mouth is not absorbed. They also point out that the cumulative effect of the above facts is to make accurate
dosage with the drug much more difficult than with sulphathiazole, and suggest that owing to its relatively slow excretion 6 hourly doses should be sufficient.

Baines and Wion (1939) however, note that as the maximum concentration is usually reached within 4 hours, 4 hourly doses should be given. They found that most of the drug was excreted in the urine, 50% being acetylated and that only very small quantities appeared in the faeces. These results, however, refer only to the excretion of a single dose, and it seems probable that when a high dosage is being given a much larger percentage may escape in the faeces, because of the relative insolubility of the drug.

Stokinger (1939a), in a study of 75 cases receiving the drug in fairly high dosage (2-6 grammes a day) found that absorption was rapid. He found that the percentage of acetylated drug in the blood is low to begin with and rises steadily for the first 24 hours when it becomes stabilised at an average of about 50% of the total circulating drug, although this percentage varies a great deal in different people.

In another paper (1939 b) he says that a blood level of 3-6 mgs. % is usually reached when 3 grammes a day is given and from 10-12 mgs. % when 6 grammes is given. These figures are rather higher than those usually found. He also mentions that some people acetylate the drug very rapidly and that this may interfere with effective treatment (1939 a).

Whitby (1939) says that the drug is absorbed to a different extent in different people. He also says that the degree of acetylation varies, and suggests that rapid acetylation
may be the reason why some people resist treatment.

Halpern and others (1939) in a recent paper, also find that the blood concentration is maximal within 4 hours and suggest a 4-hourly scheme of dosage.

It has been generally found (Graham et al./Halpern et al 1939, Whittemore et al. 1939, Meakins and Hanson 1939) that the blood concentration of M & B 693 is rarely as high as the 10 mgs. % required for effective sulphanilamide therapy. The average concentration reached is about 7-8 mgs. %, but many workers here reported cures where the blood concentration was as low as 1-3 mgs. % (Whitby 1939). These concentrations can be reached and easily maintained by the dosage recommended by the makers, namely 2 gms. on admission 2 gm. four hours later, and then 1 gm. 4 hourly until usually 20 gms. has been given.

There seems to be no advantage in having the blood concentration over 10 mgs. % (Meakins and Hanson 1939.)

M & B 693 Soluble

As I have previously mentioned (page 47), M & B 693 is very insoluble in water. This makes it unsuitable for giving by injection, as it is not absorbed. It has been found that the sodium salt is very soluble, and this preparation is now used when the drug cannot be tolerated orally. It is prepared in 3. c.c. ampoules, each containing the equivalent of 1 gramme of M & B 693 itself, and these are given intravenously, diluted to 20 c.c.s. with distilled water to maintain an effective concentration in the blood, injections are necessary four-hourly day and night.

Buttle (1939) has pointed out that because of its very rapid absorption toxic effects are likely if it is used in heavy
dosage. He suggests that it should primarily be used in the first 24 hours of treatment only, in cases where the drug cannot be tolerated orally.

The preparation has also been used by intramuscular injection. Apart from the frequency of injection which is necessary, patients frequently complain of subsequent pain. This is because of the alkalinity of the solution, its pH being 11. It can be minimized by injecting deeply into the gluteal muscles.

Whitby (1939) has found that the sodium salt is absorbed well from the rectum if given in 2% solution. Again, very frequent administration is necessary.

Toxic Effects of the Sulphonamides

As only two of these drugs, sulphanilamide and M & B 693, are now, in widespread use in this country, only their toxic effects will be discussed, although benzylsulphanilamide is still used to a considerable extent. In any case, toxic effects with this last drug are extremely unusual, hence its continued use. When any drugs, with a therapeutic action as potent as these have, are placed on the market, there is always a period of uneasiness, in case, despite careful tests for toxicity in animals, some serious toxic effect may occur, which will nullify their usefulness. This, fortunately, has not been the case with the sulphonamides, and, with reasonable precautions, the risk of serious toxic reactions is not great.

Sulphanilamide

Methaemoglobinemia

The commonest side-effect with this drug is generally
agreed to be methaemoglobinaemia thought to be the cause of a greyish cyanosis in the patient. It is very common, especially if the dosage is high, and, in such conditions, is believed by some workers to be almost constant, if spectroscopic tests are carried out (Long and Bliss, 1938a).

Marshall and Walsh (1937) think that it is probably not due to a change in blood pigment, but to a formation of pigment from condensation products of sulphanilamide in the body.

It is not a serious complication, and the general view is that it should not be regarded as an indication to stop treatment, or even to reduce the dose, if a serious condition is present. It quickly disappears when the drug is withdrawn.

However, should alarm be felt at its presence, it can be quickly cured by the oral or intravenous use of methylene blue. (Campbell and Morgan 1939.)

**Sulphaemoglobinaemia**

This is a much more serious condition than the preceding one, both in its effects, which are most marked in anaemic subjects, and in the time which it takes to disappear. It has been suggested that sulphanilamide acts as a catalyst, facilitating the absorption of hydrogen sulphide from the gut (Archer and Discombe 1937). If sulphur is taken in the diet while the drug is being given, there is an increased production of hydrogen sulphide in the gut, an increased absorption, and the appearance of sulphaemoglobinaemia. Even the ingestion of a small amount of sulphur may cause it. (Paton and Eaton 1937.)

Any increase in the fluidity of the contents of the colon also aids the absorption of hydrogen sulphide, and so any powerful
saline cathartic, whether it contains sulphur or not, will
tend to increase the normal absorption, and with the catalytic
action of sulphanilamide cause sulphaemoglobinaemia.

There seems no reason why sulphates should produce
the condition more readily than other powerful purgatives, as
their sulphur content is locked up in the sulphate ion, which
is so stable that it cannot be broken down in the body.

One theory of the catalytic action of sulphanilamide
is that the presence of its acetyl breakdown product aids the
combination of free intestinal hydrogen sulphide with haemoglobin.
(Fitch 1937.)

Cerebral Effects
Mild cerebral toxic effects, such as dizziness, headache
psychic disturbances, especially depression, and nausea and
vomiting are quite common. None of these effects are usually
severe enough to interfere with treatment.

Rashes
Morbilliform, scarlatiniform, rubelliform, erysipeloid
or urticarial rashes are quite common. While rarely of serious
significance, dermatitis has in a few cases led to exfoliation of
a generalised character. Skin eruptions are occasionally of a
petechial or purpuric type, and even in skin rashes of a mild
nature, the possibility that they are the signal of commencing
haemopoetic involvement has to be borne in mind.

Some workers believe that these rashes originate in a
photosensitivity, and that they are commonest on the exposed
parts of the body. (Menville and Archinard 1937. Goodman and
Levy 1937). In other cases there appears to be no such
photosensitivity and there is an absence of porphyrinuria. Tedder (1939) has suggested that the various pictures of sulphonamide dermatitis cannot be explained by a single theory of causation and that drug retention, sensitisation, liberation of toxins (Barber 1938, Erskine 1939) and the appearance of photosensitising agents (Rimington and Hemmings 1938) all play a part in different cases.

Drug Fever

A slight secondary rise of temperature is frequently found after giving the drug. Its cause is unknown, but it has been suggested that it may be caused by liberation of the lysed product of the bacteria (Buttle 1939). Drug fever is not in itself of importance, but must be carefully distinguished from a secondary pyrexia due to a recrudescence of the infection. In addition, it may precede the onset of some toxic reaction, such as a drug rash or an effect on the haemopoetic system. In other words, while not itself dangerous, or requiring withdrawal of the drug, it is a warning to take extra precautions.

Acidosis

This is a complication which is well-recognised, and which occurs quite frequently. Long and Bliss (1937a) found clinical acidosis in 3% of their cases. They say that it is easily prevented or cured by the administration of calcium lactate or sodium bicarbonate.

Southwark (1937) found acidosis in two of fifty cases which he treated. He studied the CO2 combining power in fifteen consecutive subsequent cases, and found a consistent though variable fall in every case.
The mechanism causing this upset is unknown, but Marshall and others (1938) believe that it is due to interference with the reabsorption of bicarbonate in the kidney tubules.

Effects on Blood Picture

Red cells

As with all new drugs, the effects on the bone-marrow have been carefully studied. A mild degree of anaemia is common, as would be expected from the fact that the drug causes porphyrinuria when given experimentally (Wien 1939). However, it is rarely severe, and often is no more than would be expected from the toxic processes due to the disease present.

Long and Bliss (1937a), however, report that in their series 3% of the cases developed a severe haemolytic-anaemia. All recovered after blood-transfusion. They consider that this is the most severe toxic effect commonly found. Three cases of severe haemolytic anaemia, occurring suddenly within a short space of time, after many cases had been treated without the complication, are reported by Harvey and Janeway. They, too, all recovered after transfusion. They had all had a large dosage of the drug, and two of them were tested after recovery with further small doses of sulphanilamide, but no further haemolysis occurred. (Harvey and Janeway 1937.)

White cells

Nowadays one of the toxic effects which is always feared with a new drug is the development of agranulocytosis.

Kracke and Parker have pointed out that the drugs which are so far known to be capable of causing agranulocytosis,
namely amidopyrine, phenacetin and certain gold salts, have
in common a benzene ring with an attached amine group, which
increases the ease of oxidation, and it was argued that in this
grouping lay their toxicity for the white blood cells. (Kracke
and Parker 1933, 1934.) Most gold salts used in medicine do
not contain a benzene ring, however, and phenacetin has been the
proved cause of agranulocytosis in only a very few cases.

Jennings and Southwell-Sander (1937) have suggested that,
as can be seen below, sulphanilamide is also a potential bone-
marrow poison, by reason of its structural formula, and advise
rest-periods, if treatment is prolonged.

\[
\text{Grouping which can cause agranulocytosis} \quad \text{Sulphanilamide}
\]

It has not yet been absolutely proved that sulphanilamide
can cause this complication, but it seems very probable that it
can. Young reports a case of acute rheumatism which had been given
54 grammes of sulphanilamide in a period of 18 days. The only drug
which had been given apart from this was sodium salicylate, which
was stopped when the sulphanilamide was started. Four days after
the withdrawal of sulphanilamide agranulocytosis developed, and
the blood, which had previously been sterile, was found to contain
\textit{Staphylococcus aureus} and \textit{Streptococcus viridans}. The patient
eventually died. (Young 1937.)

Long and Bliss had one case of agranulocytosis, which recovered on cessation of sulphanilamide (Long and Bliss, 1937a), as had the McGuires, (McGuire and McGuire 1938.)

Other Toxic Effects

Other toxic effects are rare, but peripheral neuritis, (which is relatively common with Uleron) hepatitis, nephritis and the occurrence of haemorrhagic states have been described. Bucy (1937) describes a case of optic neuritis, which occurred after only 0.5 grammes of the drug had been given, and very quickly cleared up when it was withdrawn.

Palpitation, tinnitus and paraesthesia are also described (Bottle 1939).

M & B 693

The toxic effects of M & B 693 have been widely studied but as the drug has only been generally available for about eighteen months, it is still too soon to come to any final decision about their occurrence. In his original paper Whitby found that in mice the effective dose of the drug was 66 to 8 times smaller than the average lethal dose. In other words the margin of safety was wide. He found that M & B 693 did not cause porphyrinuria, unlike sulphanilamide (Whitby 1937).

Nausea and Vomiting

In clinical practice it is generally conceded that the most important toxic action, from the point of view of interference with treatment, is the occurrence of nausea and vomiting, although the frequency of this occurrence is very different in various reports. It appears that nausea and vomiting are very
uncommon in children, and seldom interfere with treatment (Coelho 1939. Wilson et al. 1939.)

In adults the reports are very variable, and the consensus of opinion seems to be that vomiting is not a serious complication, but this is not my experience. Meakins and Hanson in a series of 30 cases found nausea and vomiting very troublesome. They state that almost every one of their cases complained of nausea and 20 of the 30 cases vomited at least once. In 3 cases the drug had to be discontinued. They found that there was no relation between the blood concentration of the drug and the onset of vomiting. They tried many ways of administering the drug to overcome this difficulty, but had no success with any. (Meakins and Hanson 1939.)

Plummer and Ensworth in a series of 111 cases found nausea occurring in 55%, nausea and vomiting in 40% and in 10% this was so severe that the drug had to be stopped. They suggest that the cause of the vomiting must be central as the drug is so bland in the mouth, and also because they never found vomiting until 4-6 grammes had been given. (Plummer and Ensworth 1939.)

On the other hand, several reports say that nausea and vomiting, though common, are not important, as they are seldom severe enough to interfere with the administration of the drug, and state that perseverance with it generally stopped the vomiting (Gaisford 1939. Graham et al. 1939.) Others find even the occurrence of vomiting a rare event, for instance Whittemore, Royster and Riedel found only two cases of vomiting in their series of thirty cases, and in these it caused no interference with treatment. (Whittemore, Royster, Riedel 1939.)
A soluble sodium salt has been tried by intravenous injection to get over the difficulty, but it is still on trial. It has, however, been useful if given by intramuscular injection. (Gaisford 1939). Whitby (1939) has found it effective given as a 2% solution per rectum.

In general other toxic effects are not common, with the exception of rashes and mental depression, and correspond more or less to those found with sulphanilamide.

**Methaemoglobinemia**

This occurs occasionally, but is not as common as with sulphanilamide. It need not cause any anxiety, and should never be allowed to interfere with treatment. (Gaisford 1939).

**Sulphaemoglobinemia.**

This complication has not so far been reported (Campbell and Morgan 1939.)

**Rashes**

Rashes, similar to those seen with sulphanilamide, occur fairly frequently. They seem to be more common with M & B 693. (Thompson 1939, Erskine 1939.) Gaisford (1939) found that they were independent of the dosage used, and quickly disappeared on withdrawal of the drug.

However, it has been shown that they may be serious, Davis (1939), describing a case of a widespread morbilliform eruption which even spread into the mucous membrane of the mouth, and ultimately caused more anxiety than the original pneumonia.

Hallam (1939) has suggested that a photosensitivity may be induced by the drug, and states that if the skin is exposed to strong natural or artificial sunlight during treatment, a
severe dermatitis may result.

Thompson (1939) has pointed out that the rashes found with M & B 693 may closely simulate measles, rubella or scarlet fever. He believes that photosensitivity is induced, and also that the patients who once develop a rash become highly sensitive to the drug, the rash reappearing immediately if the drug is re-commenced. Erskine (1939) has drawn attention to the same simulation of the acute exanthemata, and also believes that photosensitivity is present.

As with sulphanilamide, there is always the possibility that these rashes precede the appearance of more serious toxic effects, and if they occur the drug must immediately be withdrawn, and cannot again be given, at least in the near future.

**Cerebral Effects**

These seem to be commoner with M & B 693 than with sulphanilamide but the incidence reported by different workers has varied particularly in ambulant patients who are being treated for gonorrhoea. (Lloyd et al 1938a and b, Batchelor et al 1938, Prebble 1938, Bowie et al 1939, McGregor-Robertson 1938). McGregor-Robertson (1938) found headache the commonest of the toxic effects.

Headache and dizziness do not often appear to be seen in pneumonia cases, but depression seems to occur fairly frequently (Buttle 1939)

Agranat and others (1939) report a case of marked mental confusion, and Barnett and others (1939) and Meakins and Hansen (1939) report cases which became very irrational. All of them quickly cleared up on withdrawing the drug.
Effects on Blood-Picture

Red cells

Reduction in the number of red cells is not common, but a few cases of acute anaemia following the use of the drug have been reported. (Wigors (1939), Flippin (1939), Marshall and Long (1939) and Benard (1939).) These have usually followed prolonged use of the drug.

Whitby's experimental work (1938) in mice, which has recently been confirmed by Wien (1939), makes it unlikely that anaemia should be common. He demonstrated that, in contrast to the finding, with sulphanilamide, the drug does not cause porphyrinuria. This makes it unlikely that there is a toxic effect on the red bone-marrow, as such an effect almost always leads to an increased excretion of porphyrins in the urine from an interference with the building up of haemoglobin. (Chandler et al. 1939.)

White cells

The effect of the drug on the white cells has been very carefully studied. Like sulphanilamide M & B 693 contains a benzene ring with an attached amino group, and is therefore, according to the hypothesis of Southwell-Sanier (1937) mentioned above, a potential bone-marrow poison.

\[
\begin{array}{c}
\text{NH}_2 \\
\text{SO}_2 \\
\hline
\text{NH}
\end{array}
\]

\[\text{M} \& \text{B} \ 693\]

It has been found that a reduction in the number of white cells does occur, but only rarely, and usually after
prolonged use of the drug in high dosage. Definite agranulocytosis has occurred, there being 8 cases on record to date. (Johnson (1938), Coxon and Forbes (1938), Agranat et al (1939), Barnett et al (1939), Paillas et al (1939). Sutherland (1939), Graham et al (1939) Nicol and Freedman (1939).) Of these cases, three (Johnson, Paillas, Nicol and Freedman) were fatal. In addition, Crofton (1939) has reported three cases of marked granulocytopenia during treatment for pneumonia and Rosenthal and Vogel (1939) have reported a case of monocyte granulocytopenia, which recovered and a fatal case of lymphocytic granulocytopenia.

All of these cases followed prolonged use of the drug in high dosage. It would seem advisable, in the light of these cases, that, if the dosage of the drug is prolonged for more than a few days, daily white-counts should be done to exclude the possibility of this very dangerous complication.

Action on Kidney

As I have mentioned in the section on the excretion of M & B 693, 50% of the drug in the urine is usually in the acetylated form. It has been shown that, with a high dosage of the drug, it is possible for precipitation of this acetyl derivative to occur in the kidney and ureters, with consequent irritation of the renal tract by the jagged crystals, and haematuria. (Stewart et al (1936) Antopol and Robinson (1939), Gross and Cooper (1939).) Many clinical reports have appeared of haematuria during drug treatment (e.g. Robertson (1938) Hanssen (1938), Graham and others (1939). A clue to the conditions necessary for precipitation is given by Backhouse (1939) who had no fewer than 13 cases of haematuria in 109 Polynesian natives. In one case without haematuria small calculi were found obstructing both ureters. Commenting on
this high incidence he suggests that it was due to the fact that his patients had a concentrated, highly acid urine, because of the great heat, and that it was impossible to ensure an adequate fluid intake.

This suggests that this complication, which is relatively uncommon in this country, is best avoided by maintaining a high fluid intake, when a high dosage of the drug is being given, particularly if the patient is sweating or vomiting a great deal and the urine is tending to become concentrated.

If vomiting is so severe that the onset of this complication is feared, it would seem advisable to give fluid intravenously or per rectum.

**Acidosis**

Clinical acidosis has not so far been reported.

**Hepatitis**

In view of suggestions that this might be a possible complication, Whittemore and his colleagues (1939) did serial icteric indices on eight of their pneumonia cases, and could find no evidence of liver damage. In seven of the cases the icteric index actually fell during treatment.

**Drug Fever**

As with sulphanilamide, it is generally found that this is quite common. If it does occur the observations made on its appearance with that drug hold good, i.e. that (a) it must be carefully distinguished from a recrudescence of the infection and (b) that it may herald more serious toxic effects.
**Active Principle of Sulphonamides.**

In his original publication Domagk (1935) pointed out that prontosil has a very slight antistreptococcal effect in vitro. It is remarkable how inactive this drug is chemically. (Nesse and Hecht 1935.) In 1935 Tréfouël and others, working in France suggested that sulphanilamide was the active principle, and that the coloured azo compounds were reduced to this substance in the body. (Tréfouël et al. 1935-6) Gley and Girard (1936) disputed this, saying that they could find no sulphanilamide, azo dye or triamino benzene in the urine of animals being given prontosil by mouth, but later work has proved them wrong, (Fuller 1937.) (Long and Bliss 1937 (a)) and it is now generally agreed that sulphanilamide is produced in the body when prontosil or prontosil soluble is given.

Their suggestion that sulphanilamide is actually the active principle has not been wholly substantiated. It has been shown that while sulphanilamide may be an active principle there must be other ones. Long and Bliss (1937 a) showed that while prontosil itself has no action against haemolytic streptococci in vitro, when reduced to sulphanilamide with cysteine hydrochloride it has. Colebrook and others (1936) had already shown that serum and prontosil were inactive against streptococci, but that serum plus sulphanilamide rapidly caused death of the organisms. Hoare (1938) and Osgood (1938) also showed that serum plus sulphanilamide in low concentration had a marked bactericidal effect on haemolytic streptococci. All this work goes to prove that sulphanilamide is an active principle. However, Gley and Girard (1936) showed that azo dyes containing
Sulphanilamide can have an action much stronger than would be expected from the amount of that substance in them. This suggests that their action cannot solely be due to their contained sulphanilamide. (Page 43).

As I have already mentioned, Buttle and others (1937) demonstrated that two diphenyl sulphone compounds are active against the streptococcus and the pneumococcus. Also Fourneau and others (1937) showed that dinitrodiphenylsulphide and dinitrodiphenyldisulphide are effective and Hoerlein (1937) states that para benzyl amino phenyl sulphonamide and para amino phenyl sulphonamido phenyl sulphonamide (diseptal C) have been proved to be active against streptococci. The importance of these findings is that the above substances cannot be broken down into sulphanilamide in the body, proving that some active principle apart from that substance, must exist.

It may here be mentioned that the acetyl conjugation product of sulphanilamide, para acetyl amino benzene sulphonamide, has been shown to have practically no action against the streptococcus (Goissedet et al. 1936 Marshall et al. 1937) so little help can be gained solely by a study of the products of excretion.

An interesting suggestion is advanced by Buttle (1939) who considers that the products formed by substitution in the amino group of sulphanilamide namely prontosil, prontosil soluble, rubiazol, proseptasine and soluseptasine, owe their action to a splitting into sulphanilamide and its acetyl compound. Substances on the other hand, which are formed by substitution in the amide group, such as uleron and M and B 693, he suggests are themselves active agents and are not split into sulphanilamide in the body.
He therefore postulates many different active principles.

As to what constitutes the active principle of M and B 693, little is known apart from the suggestion made above that it is itself an active principle. Browning (1939) in a review of the present position, says that there are great gaps in our knowledge, and agrees with the suggestion that M and B 693 is probably itself the active principle, unless more active compounds are formed from it in the body, a hypothesis of which we have at present no proof.
Mode of Action of Sulphonamides

As I have mentioned in the previous section sulphanilamide has been shown by some workers to have a definite antibacterial effect in vitro. (Colebrook et al. 1936, Long and Bliss 1937 a, Hoare 1938, Osgood 1938.) However, all of these workers found it necessary to include in their culture media human cells or serum or both. This suggested that the action of sulphanilamide was not simply bactericidal, but that it was somehow connected with the natural defences of the body. A great deal of work has been done to discover the nature of this mechanism and many theories have been advanced. The most recent work has tended to throw doubt on the importance of the body's defences, and suggests that the action may be bactericidal after all, or at least that the main action of the drug is on the organisms with the leucocytes only playing a secondary part.

The exact mode of action of M & B 693 is just as undecided as is that of sulphanilamide but the general trend of recent work suggests that the mechanism is probably very similar in both cases, as would be expected from the fact that the former drug is a close chemical relative of the latter.

One of the earliest ideas as to the mode of action of the sulphonamides was that of Levaditi and Vaisman, who, in a series of communications in 1935 and 1936 (1935 a, b, 1936) suggested that the drugs prevented encapsulation of the streptococcus in the tissues, and so favoured phagocytosis. In 1937 (b.c.) Long and Bliss examined hourly peritoneal smears from mice which had been infected with streptococci and given sulphanilamide.
The organisms multiplied and remained virulent for 6 - 15 hours and then large numbers of polymorphs appeared and ingested them, later many lymphocytes were also seen. They suggested that phagocytosis first by polymorphs and later by lymphocytes, played the major role in the destruction of the organisms. They believed that the streptococci were damaged by the sulphanilamide and their growth hindered. They were unable to confirm the non-capsulation theory of Levaditi and Vaisman, mentioned above.

In opposition to this theory Domagk (1937), using prontosil found that the peritoneal cavity of mice infected with streptococci appeared normal a few hours after giving the drug and that there was no evidence of phagocytosis. Mellon and others (1937), using sulphanilamide, found no evidence of phagocytosis in smears from the peritoneal exudates or sections of liver and spleen in similarly infected mice. Browning (1939) in a review of the question, mentioned that he was able to confirm Mellon's results, and suggested that the chief action of the drug is to alter the reactivity of the host, so that highly virulent organisms are treated by the body in the same way that it would react to non-pathogenic organisms normally. In other words, the consensus of opinion at the moment has swung away from the theory that phagocytosis is the main mechanism involved.

Lockwood (1938) has recently made a suggestion which has many supporters. He found, working in vitro, that traces of peptone in the culture medium interfered with the bacteriostatic and bactericidal action of sulphanilamide on streptococci. If these organisms were washed free from peptone before adding
sulphanilamide bacteriostasis occurred and the organisms died, quite independent of the presence or absence of phagocytes.

He suggests that the action of sulphanilamide on streptococci is after all a direct one, the drug interfering with their protein metabolism. If peptone is present, they are saved by the use of that. He also points out that his theory is supported by the clinical observation that where there is a large amount of peptone and other protein breakdown products in the tissues the action of sulphanilamide is greatly hampered. This occurs, for instance, where there is an abscess.

The most recent theory is another which implies that sulphanilamide acts by interfering with the metabolism of organisms. Locke and others (1939) suggested that when pneumococci die in the presence of sulphanilamide the actual cause of their death is hydrogen peroxide. They believe that the drug inhibits the production of catalase and so allows the accumulation of hydrogen peroxide. They showed, by exposing solutions of sulphanilamide to low-intensity oxidation produced by ultra-violet light, that anticatalase was produced in the solution. Main and Shinn (1939) have pushed the theory further by showing that when growth retardation is produced in cultures of type 1 pneumococci containing sulphanilamide there is a preceding rise of peroxide content.

This theory was called in question by an editorial in the Medical British Journal (1939) which points out that Fuller and Maxted (1939) have studied the capacity of 75 strains of streptococcus to form peroxide. They found that Griffith's type 3 is quite unable to do so. According to the theory just mentioned, this
streptococcus should obviously be insensitive to the action of sulphanilamide, but this is very far from being the case. It is suggested that if sulphanilamide cannot act on this organism by inhibiting catalase, it is very doubtful if its activity against other streptococci or pneumococci can be due to this mechanism.

Locke (1939) in a reply to this, admits that these findings cannot be commented on at the moment and says that they are being investigated experimentally. He suggests that Lockwood's theory, mentioned above, of an effect of sulphanilamide on the protein metabolism of streptococci must be considered as a secondary result of peroxide accumulation, if it is not a primary one.

As can be seen, the question of the exact mechanism of sulphanilamide's action against organisms is very far from settled, but the general trend at the moment is to regard its action as being primarily antibacterial, through an interference with the organisms' metabolism.

The action of M and B 693 has also been widely studied, and the position is rather similar to that with regard to sulphanilamide. No finality has been reached, and the present theories seem rather preliminary concepts than completed investigations. The drug, after all, has been in use for too short a time to study such matters adequately. However, there have been many interesting suggestions.

Professor Fleming (Fleming 1939 (a) (b)) after a series of experiments, has come to several conclusions as to the probable mode of action of M and B 693. He has found that the blood of patients receiving the drug is definitely strongly
bacteriostatic to the pneumococcus, but that it is not bactericidal. He finds that this bacteriostatic power lies in the serum of the blood, and that the efficiency of the leukocytes is not increased. The drug does not prevent encapsulation of the pneumococcus, but, in addition to its bacteriostatic action, prevents the production of substances by the organism, which cause changes in the blood in culture. He suggests that the action of the drug may be to favour phagocytosis, without promoting any leucocytosis, by relatively disabling the organism through bacteriostasis and by inhibiting its production of the toxins with which it defends itself against leucocytosis. He considers that therefore the immune state of the body plays an important part and suggests that immune sera and vaccines should be given along with the drug.

His statement that capsule formation is not interfered with is supported by some work done by Stacey and Schluchterer (1939), who found that M and B 693 has no effect on the capsular polysaccharides of the pneumococcus. They suggest that the drug may interfere with the supply of an accessory growth factor, allowing the organism to be killed by phagocytes, but add that the problem needs a great deal of further study.

McIntosh and Whitby (1939) have found that the drug neither stimulates leucocytosis nor influences the quality, quantity or rate of production of specific antibodies pneumococcus. The immunity developed in mice after an attack of pneumonia treated with M and B 693 is type-specific, in spite of the fact that the drug acts on all types of pneumococci, varies directly with the size of the infecting inoculum, and is just as active as the immunity produced by inoculating the animals with a large dose
of killed pneumococci. For instance, mice which survive inoculation with 10,000 lethal doses of pneumococci, having been treated with 30 mgs. of M and B 693, are, one week later, completely immune to a second inoculation with as much as 1,000,000 lethal doses without further treatment. Schmidt and Hilles (1939) have recently confirmed these findings.

This work, therefore, suggests that the drug has an entirely passive action with regard to the body's defence mechanisms, neither stimulating nor inhibiting them. They also find that mice immunised with killed pneumococci and given a course of M and B 693 are not more effectively immunised. This work conflicts with that of Fleming (1939 a. and b.), De and Basu (1938), Loewenthal et al (1939), Eve (1939) McLean (1939), Powell and Jamieson (1939) and McElligott and Cokkinnis (1938), who all claim to have found, in various ways, that stimulation of the bodily defences by other means augments the action of the drug.

In the same extremely interesting paper McIntosh and Whitby have shown that in mice treated prophylactically or after inoculation with M and B 693 the capsule begins to show changes such as swelling and crenation of its edge in about 2 hours. After 4 hours most of the organisms show this change, and later a large number of organisms seem to lose their capsules altogether. However, they have not been able to demonstrate any loss of type-specificity in these organisms, and, in addition, organisms cultivated from the blood-stream late in a treated infection have shown neither loss of capsule nor virulence.

Reid (1939) has also recently shown that M and B 693 has no effect on capsules or type-specificity of pneumococci in a period of 24 hours. Hoyt and Levine (1939) have also been unable to
demonstrate any inhibition of the capsules.

McIntosh and Whitby believe that this phenomenon, which they have only been able to demonstrate in mice after intra peritoneal inoculation, may just as easily be nothing more than the final process by which the body rids itself of dead pneumococci, as due to a primary action of the drug on the organism.

In addition, they have found several peculiarities in the action of the drug in mice, which help to indicate its mechanism, and which must be explained in any hypothesis advanced on the subject.

(a). Lag in action.

They have found that, whether the drug is given prophylactically or at the time of inoculation, multiplication of inoculated pneumococci in the peritoneum of the mouse goes on for a few hours. As this occurs when the drug is given prophylactically it cannot be due to a lag in absorption of the drug.

They have even found that multiplication of the organisms for the first few hours is usually faster in animals treated with the drug, than in controls where it is withheld.

In addition, they find that invasion of the blood-stream following intra-peritoneal inoculation occurs under the same conditions and that the multiplication of the organisms in the blood goes on for at least seven hours. In animals which recover the blood-stream is clear in 24 hours. This is in contrast to the entire absence of blood-stream invasion in animals protected with Felton's serum or which have had a previous infection cured with M and B 693.
It is therefore obvious that a certain time is necessary before the drug becomes effective.

(b). Quantitative action.

They have found that there is a definite quantitative relationship between the effective concentration of the drug and the number of bacteria which can be overcome. The limit of activity of the drug in a concentration of 16 mgs %, is between 50,000 and 150,000 organisms.

They have also been unable to find any absorption or fixation of the effective substances by the bacterium in vitro, as, even with very large numbers of organisms, no appreciable loss of the drug could be determined.

(c) Phase of Organism.

The action of the drug is found to be very strong on young, actively growing pneumococci. On old, sub-cultured, "rough" organisms, there was no action.

(d) Action in Different Media.

Comparing the action of M and 3 693 and sulphanilamide in different media against streptococci and pneumococci, they found that both drugs are inactive against streptococci in peptone broth but active against pneumococci. This, incidentally, confirms Lockwood's (1939) work on the streptococci.

To explain the above phenomena they advance a theory of action, which agrees with and supplements the hypothesis of Lockwood (1938) and Locke, Main and Mellon (1939).

In the first case, they suggest that the lag in action and differentiation of the phase of the organism rules out any conception that the drug may act as a simple germicide. In particular the
fact that the organisms often multiply faster for a few hours in treated animals makes this extremely improbable.

They believe that the lag in action indicates a slow combination or neutralisation of the drug, operating on some essential food substance or enzyme of the organism. The idea that combination or neutralisation occurs is suggested by the quantitative relationship between drug and organism. They also believe that the lack of action of the drug on avirulent organisms is because these have much less exacting food-requirements.

They do not however, explain how this suggestion that combination or neutralisation occurs, agrees with their finding that there is no absorption or fixation of the drug by bacteria in vitro.

To explain the fact that sulphanilamide and M and B 693 have no action on the streptococcus in a medium containing peptone, and yet are both active against pneumococci (sulphanilamide much less so) in such a medium, they suggest that, in the case of the streptococcus in the presence of sulphanilamide or M and B 693, peptone supplies something to the organism, which blood lacks, while with the pneumococcus, both peptone and blood lack something which is essential to the organism.

Since peptone inhibits the action of these drugs on streptococci but not on pneumococci, it is obvious that the mode of action on the two organisms must differ, if not in principle at least in detail.

Summing up, they believe that while it is hardly conceivable that, in such an excellent medium as an animal's blood-stream, an actual food factor is destroyed, or fixed, it is conceivable that the bacterial enzyme, of which this food factor is the substrate
is inactivated. They mention that this belief is supported also by the known lack of action of the sulphonamide drugs on viruses, which have a very feeble enzymatic action.

It is interesting that some work has already been done in America to apply Locke's theory of peroxide accumulation to the action of M and B 693. McLeod (1939) has demonstrated a falling off in ability to produce peroxide in pneumococci which have developed a "fastness" to the drug. He suggests that M and B 693 damages the dehydrogenase system of the pneumococcus, instead of or in addition to, inhibiting the production of catalase.

Hoyt and Levine (1939) have shown that peptone causes a marked interference with the action of M and B 693 against a type II pneumococcus, and in later publication the same workers, with Larson and Bieter, (Larson et.al. 1939), have found that it is the amino acids in peptone which contain aromatic groups, which cause this interference. They suggest that peptone may interfere with the action of M and B 693 through interfering with the absorption of the drug on to the surfaces of the bacteria.

From the review, given above, of the experimental work which has been done to elucidate the mode of action of M and B 693 and sulphanilamide it can be seen that opinion is rapidly crystallising and that the various theories propounded are not inconsistent, but rather different aspects of the same mechanism.

It is generally agreed that the main action of the drugs is bacteriostatic, by interfering with the food supply of the organism, which is thus greatly weakened or even possibly starved to death. The researches of Lockwood and Locke and others in America are concerned with the minutiae of the biochemical way in
which this bacteriostasis is brought about. In England the main point at issue seems to be the importance of the role played by the bodily defences once the organism has been weakened by the drugs, Whitby and his associates tending to stress the activity of the drugs and minimise the immunity mechanisms, while Fleming and followers give the first place to these, and stress the importance of raising them to the highest possible level by means of vaccines and sera.

Objections could be raised however to the validity of applying conclusions drawn from some of the experimental investigations of Fleming and co-workers to the chemotherapy of spontaneous infection in man. For instance, in one experiment Fleming gives a vaccine to mice before inoculating them with pneumococci and giving them M and B 693, and concludes from this that vaccines should be helpful in human infections. Fleming (1939 b).
Treatment of Acute Lobar Pneumonia by
M and B 693.

Drug Therapy.

The preparation used in this investigation was M and B 693 (May and Baker) in the form of 0.5 Gm. tablets. The dosage adhered to was that suggested by the makers, namely four tablets on admission, four four hours later and then two tablets four hourly until 48 hours after the temperature had fallen to normal. The drug was not reduced gradually, but was stopped abruptly. In an ordinary case the dosage was kept below the maximum of 40 tablets suggested by the makers, but in a severe case no hesitation was felt in continuing the drug past that, keeping a careful watch for toxic effects.

No cases were used as controls (a) because the small number of lobar pneumonias admitted did not permit of it, and (b) because it was felt that it would be quite impossible from the humanitarian standpoint, to withhold the drug, which I was soon convinced was very efficacious, from any seriously ill patient.

Adjuvant Treatment.

The usual adjuvant treatment was given in addition. Morphia, in doses up to grs. $\frac{1}{2}$ was given unhesitatingly, if pleural pain was preventing sleep. In no case, I am convinced, did this do any harm, and in many cases it did a great deal of good. The patient slept well, and felt much better the next morning. Kaolin poultices were also used for the relief of pain, and proved very soothing. Expectorant cough mixtures were not given, as it was soon found that M and B 693 had a tendency to cause nausea and
vomiting which was increased by these mixtures. For that reason no drugs, apart from the M and B tablets were given by mouth, if they could be avoided. The diet was kept light, consisting mainly of milk. Glucose drinks were given as desired, unless they were found to encourage nausea.

The greatest difficulty in treatment was found to be a tendency to vomit caused by the drug. Actually six of the 23 cases vomited, two so severely, that although attempts were made to continue with the drug so little was retained that it lost all therapeutic value, (Cases VI and XI) and a third in which it had to be stopped when only 10 Gms. had been given (Case X). Fortunately in this case the temperature had fallen to normal and remained there.

If vomiting occurred, the tablets were broken up in milk flavoured with lemon juice, but this was not found very helpful, as the gritty feel in the milk was found to be very unpleasant. Sodium bicarbonate was given in doses of grs. XXX just before giving the tablets, but was not found to be of any value. A mixture consisting of acid hydrocyan. dil III sod. bic. grs X and aqua menth. pip. ad fl. oz. ss was tried if the above measures failed, but was of little use.

In two cases who were very ill and vomiting (VI and XI), a preparation for intramuscular injection was tried. As it contained only 0.5 Gm. of the drug in 2.5 c.c's. of oil it was found impossible to inject enough to keep up an adequate concentration in the blood; it had no clinical effect, and treatment had to be abandoned in both cases. Fortunately, both eventually recovered. The most that could be injected without causing a great deal of pain
was 15 c.c's. in the day, containing only 1.5 Gm. of the drug. This could obviously have no therapeutic effect, so after these two cases the preparation was not used. In other words, if severe vomiting occurred it was found that the only way to stop it was to discontinue the drug.

Persistence with the drug certainly had no effect in lessening nausea in my cases.

Serum was not used as it was felt that it would tend to make it more difficult to assess the value of the drug, except in one desperate case which died a few hours after admission.

Routine Investigations.

Certain investigations were carried out as far as possible on all cases. A routine procedure was devised, and followed more or less faithfully.

(a) Before giving the first dose of M and B 693 two specimens of sputum were obtained. The first was examined by me in the hospital laboratory, and if it contained pneumococci these were typed, using Lederle's typing sera. The second was sent up to the laboratory of the University of Edinburgh for confirmation. In several cases I found it impossible to type the pneumococci directly, and they were typed at the University, using the mouse inoculation method.

(b) Also before giving M and B 693 a white count was done. After this, white counts were done daily until at least two successive ones were inside the normal limits.

(c) In severe cases a blood-culture was done, and was repeated three times, at daily intervals. In all the twenty-three cases only one positive blood-culture was obtained, and
that was done by myself on blood agar. (Case XVII). It seemed that if blood was sent up to the University laboratory the organisms died before they were plated out.

(d) A portable X-ray of the chest was done as soon as possible after admission to confirm the diagnosis. Further X-rays were carried out if progress was not satisfactory and in all cases one was done before discharge to make certain that the chest was clear.

(e) In the earlier cases daily erythrocyte sedimentation rates were performed but it was found that they were not of much value and that the patients came to dread the daily prick of the intravenous needle, so they were abandoned.

Five of the cases were treated in the wards of my colleague, Dr. John Guthrie, and I am very grateful to him for allowing me to include them. They were cases I, II, IV, XX and XXIII. The scheme of dosage was the same as in my cases, but in some of them all the routine investigations were not carried out. In particular, case I was not X-rayed.
As I have already mentioned, the subject of this investigation is the treatment of 23 cases of acute lobar pneumonia, admitted to the Western General Hospital, Edinburgh between October 1938 and April 1939. No case was included unless the diagnosis appeared to be almost certain. Broncho-pneumonia and cases occurring in children under 10 years old were excluded. The diagnosis in every case was based on a careful clinical examination, supported by the evidence of a white blood count, a bacteriological examination of the sputum and a portable X-ray of the chest.

No control group was possible, and so some criteria had to be fixed, by which the efficacy of the drug could be judged. These were as follows.

(a) The case - mortality, as compared with the usual statistics given in the standard text-books.

(b) The rapidity of clinical improvement, as evidenced by a fall of temperature and diminution of toxaemia, compared with the usual course of the disease.

(c) The rapidity of resolution of clinical signs in the chest.

(d) The incidence of complications, compared with their usual frequency.

Two of these criteria, (a) and (d), cannot have too much stress laid upon them, because of the small number of cases involved. However, they will at least give some indication of the effect of the drug, especially if they differ widely from the usual findings.

It is on the other two, (b) and (c) that most reliance must
be placed, as in their case, if the results are at all consistent, the number of cases seems sufficient to discount largely the effects of coincidence.

Following the method used by Evans and Gaisford in their publication (1938), I have summarised my cases in the form of protocols, discussing some of the cases with special points of interest in more detail later. The severity of the attack has been indicated by one, two or three + signs, and the part of the lung affected by the initials of the lobe or lobes. For example, the right lower lobe is shown as R.L.L.

It will be noted that no fewer than 15 of the cases are given three + signs. This is because, in general, only seriously ill cases are sent into hospital. The others are treated at home by their own doctors. This makes the series more valuable in assessing the value of a new treatment.

In column 5 of the protocols the expression "day of illness" is used. This is meant to indicate the day of the illness that drug therapy began, and not the day of admission.
<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>Lesion</th>
<th>Day of Degree</th>
<th>Day of Illness</th>
<th>Pre-existing Illness</th>
<th>Total Dosage</th>
<th>Effect</th>
<th>Toxic Complications</th>
<th>Re-Organism</th>
<th>Effects of Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>M</td>
<td>58</td>
<td>R, U, L.</td>
<td>4th ++</td>
<td>6th +</td>
<td>Arterio-sclerosis 22.5</td>
<td>Temperature fell: None</td>
<td>None</td>
<td>Died: Strep-tococcus viridans</td>
<td></td>
<td>Recovered:</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td>sputum collected: 24 hours</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Coronary artery disease</td>
<td></td>
<td></td>
<td>then suddenly died: 24 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>M</td>
<td>15</td>
<td>L, I, L.</td>
<td>3rd + +</td>
<td>3rd None</td>
<td>Systolic: Type I</td>
<td>Temperature fell: None</td>
<td>None</td>
<td>Cured: Pneumococcus</td>
<td></td>
<td>Clinical improvement:</td>
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<td>F</td>
<td>15</td>
<td>L, U, L.</td>
<td>4th ++</td>
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<td>Systolic: Type XXII</td>
<td>Temperature fell: None</td>
<td>None</td>
<td>Cured: Pneumococcus</td>
<td></td>
<td>Clinical improvement:</td>
<td></td>
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<tr>
<td>No.</td>
<td>Sex</td>
<td>Age</td>
<td>Lesion</td>
<td>Day of Illness</td>
<td>Degree of Illness</td>
<td>Temperature</td>
<td>Treatment</td>
<td>Complications</td>
<td>Organism</td>
<td>Effects</td>
<td>Symptoms</td>
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<td>V</td>
<td>F</td>
<td>50 L.L.</td>
<td>2nd</td>
<td>+ + +</td>
<td>Obesity, High Blood Pressure</td>
<td>38.5</td>
<td>Palliative</td>
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<td>None</td>
<td>None</td>
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<td>F</td>
<td>40 R.L.</td>
<td>2nd</td>
<td>+ +</td>
<td>High Blood Pressure, High Blood Sugar</td>
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<td>Palliative</td>
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<tr>
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There were three fatal cases in the series, and their case-histories will first be summarised below.

Case I was a man of 58 who was admitted on the 4th day of his illness, with consolidation in his right upper lobe. His sputum was not examined for 24 hours after admission, and the only organism then found was a streptococcus viridans, which was presumably a secondary invader. He responded satisfactorily to M and B 693, his temperature falling in 48 hours, with marked clinical improvement. His total dosage was 22.5 grammes.

Eight days after admission he suddenly had a very severe heart attack with substernal pain, and died very rapidly presumably from coronary thrombosis. At that time there was only a little dullness remaining in his chest, and he appeared to have quite recovered from his pneumonia. His radial arteries were markedly arteriosclerotic. Permission for a post-mortem was refused.

Case XII was a woman of 57 who was admitted moribund on the 4th day of her illness, with the signs of consolidation in her right lower lobe, and marked congestion in the remainder of both lungs. Her sputum contained many staphyloccoci of the aureus type and also a few type 2 pneumococci. Her white count was only 5,900 on admission and fell rapidly to 1,500 before death.

She was given a total of 4 grammes of M and B 693 and also 10,000 units of Lilly's type 2 antipneumococcal serum intravenously, without any beneficial effect. She died only 9 hours after admission. A post-mortem was not obtained.
Case XVIII was an old man of 74 who developed an empyema subsequent to his pneumonia. He suffered from auricular fibrillation, and died from exhaustion three weeks after rib-resection. Permission for a post-mortem examination could not be obtained. A type 5 pneumococcus was found in his sputum.

His case is more fully summarised under the heading of cases which developed an empyema.

It can be seen from the above that none of the deaths can be put down directly to a failure of M and B 693, as one died of coronary thrombosis after recovering from his pneumonia, the second was moribund on admission and the drug had no chance, and the third, an old man of 74 with auricular fibrillation, died after an empyema and a long exhausting illness.

Although the series is too small to lay much stress on statistics, it is highly encouraging that no case, although many of them had the disease in a severe form, died owing to a failure of the drug.

Other reports of experiences with the drug confirm these findings. Evans and Gaisford (1936) in their series, had a mortality of 8% in 100 treated cases, compared with 27% in 100 controls. In the large South African series (Agranat et al. 1939) the death-rate in the treated cases was 3.5% and in the controls was 10%. If the cases previously vaccinated are excluded the figures become 4% and 12% respectively. The morality of the control series is much less than that generally, found in this country, the figure given by Prices Textbook of Medicine being 25 - 27%. This agrees with the findings of Evans and Gaisford.

In Canada Graham (1939) had a mortality of 3.3% in 30 cases,
compared with 23.3% in 30 controls. The addition of a further 20 treated cases, without controls, raised his death-rate to 6%.
Both of the deaths in the additional series were in patients over the age of 60.

The number of references could be multiplied greatly but all show similar results, namely a very definitely decreased mortality in cases treated with the drug. Marriot (1939) has recently analysed the mortality of 1991 cases from the literature. Of these 110 died, giving the remarkably low fatality-rate of 5.5%. Such a figure leaves no doubt that a most effective agent against the pneumococcus has been discovered.
Effects of the Drug.

Temperature.

The most obvious effect of the drug was the dramatic fall in temperature which occurred shortly after giving it. In 16 of the cases it had fallen to 98.4°F or lower within 24 hours and in 4 more within 48 hours. Of the remaining 3 cases, 2 had reached a normal temperature in 60 and 72 hours respectively, and the third died 9 hours after admission.

As a normal crisis does not usually occur until about the 7th day of the disease the falls of temperature encountered can scarcely be explained as even premature crises, since the fall took place on the 3rd day in 5 cases, on the 4th in 7 cases, the 5th in 2 cases and the 6th in 4 cases, making a total of 18 cases in which the temperature fell before the 7th day. Of the remaining 5 cases, 2 had a fall of temperature on the 7th day, 1 on the 9th and another on the 13th day, the remaining case dying 9 hours after admission. In the cases in which the temperature did not fall until the 9th and 13th day, vomiting was so severe that the drug was absorbed in negligible quantities, and had no chance of having any effect. The fall of temperature which was encountered so regularly and rapidly would therefore appear to be a direct result of the action of the drug on the infection.

In common with most other workers, I found that a secondary rise of temperature was quite common after the initial fall. Excluding the 3 cases who developed empyema, it occurred in 9 cases. In two of these, XI and XVI, an extension of the disease occurred, in case XI because vomiting was so severe that practically none of the drug was absorbed, and in case XVI because only 5 grammes of the
drug was given, for a reason which will be explained later. In the other 7 cases the temperature was back to normal within 24 hours and caused no apparent inconvenience to the patients. There did not seem to be any exacerbation of the disease in the chest while the temperature was raised. The conclusion arrived at was that this secondary rise of temperature was without significance, and could be disregarded.

Clinical Improvement.

Again in common with the usual finding, clinical improvement was slower than the fall of temperature, which in 9 cases actually caused an increase in symptoms and collapse. (Cases IV, V, XI, XII, XIV, XV, XVI, XIX and XX).

Whereas 16 cases showed a fall of temperature to normal within 24 hours, only 5 showed clinical improvement in the same time. Eight improved in 48 hours and 7 in 72, leaving cases VI and XI, who vomited so severely that the drug had no action and case XLI, who died just after admission.

However, clinical improvement was markedly faster than it would have been without the drug, as 15 cases showed marked improvement before the 7th day of the disease, 2 on the 3rd day, 4 on the 4th, 7 on the 5th and 2 on the 6th. Three further cases improved on the 7th day.

These effects of the drug have been generally found, the fall of temperature in most cases being dramatic. The period of hospitalisation is also greatly reduced.

Gaisford (1939) having treated between 600 and 700 cases with the drug, states that the temperature returns to normal within 48 hours of giving the drug, and goes so far as to state that
continuance of pyrexia after a drop indicates either the presence of some complication, or that the infecting organism is not a pneumococcus. This statement, however, seems rather sweeping in the light of some recent work by McLean, Rogers and Fleming (1939). They have found that occasional pneumococci are resistant to the drug, some highly so, and that this resistance occurs in strains and not types.

Another interesting observation which they made was that, if the dosage of the drug were low, the pneumococcus might develop a definite resistance or fastness to M and B 693. They therefore suggested a high initial dosage in all cases. This work has been confirmed clinically by Anderson (1939).
Resolution of the Pneumonia

This did not seem to be hastened or delayed by the use of the drug, the signs in the chest disappearing at about the same rate as would be expected in a case treated without it. No cases of delayed resolution were encountered. It is strange that, in spite of the dramatic effect of the drug on the temperature and toxaemia, the local signs in the chest should persist, but this has been the general experience.

For example, Nilson and others (1939) found that X-ray densities in the chests of 12 cases treated with the drug disappeared at the same rate as in controls. Evans and Gaisford (1938) note that they encountered 2 cases of delayed resolution in the 100 they treated. This does not seem by any means an excessive proportion (Osler 1938a). In a further series of almost 700 cases (1939) Gaisford states that there seems to be no alteration in the rate of resolution of cases treated with the drug, but add that in a few cases it actually appears to be delayed.
Cases which developed Complications.

Cases which developed complications will now be summarised, and an attempt made to assess the frequency of these as compared with cases treated without the drug. In the series of 23 cases there were three empyemata and one otitis media.

Otitis Media.

Case XI was a man of 33 who came in on the 5th day of his illness with consolidation in his right middle lobe. With the beginning of his pneumonia he had also developed an acute otitis media in his left ear. This had apparently subsided on admission.

As he was such a late case, and there was only a little dullness in his chest he was not put on M and B 693, and the next day appeared to have improved spontaneously. The following day, however he became very much worse, and an X-ray of his chest showed an extension to his lower lobe. He was therefore put on full doses of the drug. At this stage his white blood count was 20,000 and his sputum contained many type 5 pneumococci.

He began to vomit 24 hours after the drug was begun and in spite of giving the tablets ground up in milk and adding sodium bicarbonate, continued to do so. Injections of the drug, 0.5 grammes suspended in oil, were given, but appeared to do no good and were stopped after three days. He had a total of 19 grammes, but it is very doubtful if much was absorbed.

During this time his pneumonia extended until it involved practically the whole of his right lung. After the drug was stopped he slowly improved, but there was an exacerbation of the infection of his ear, his drum ruptured and it began to discharge. Unfortun-
ately the pus was not examined, so it is not known whether it was pneumococcal or not. After this he progressed well, and was discharged cured.

Empyema.

Case XII was a man of 43 who was admitted on the 5th day of his pneumonia his right lower lobe being affected. His sputum was brightly blood-stained and contained only Friedlanders pneumobacilli. He was very ill and was immediately put on M and B 693. His temperature fell rather slowly, reaching 98°F. in 48 hours, and he improved clinically. The drug was stopped after 32 grammes had been given, six days after admission.

Three days after admission his temperature rose again, and he developed an empyema in his right pleural cavity. The pus contained a few Friedlanders pneumobacilli in a film, and a pure culture of the organism was grown from it.

He was treated by operation and open drainage and made a complete, though slow, recovery.

Case XVII was a woman of 49, admitted on the 2nd day of her pneumonia with consolidation in her right middle and lower lobes. She was very ill indeed, her sputum contained many type 8 pneumococci and blood-culture was positive, type 8 pneumococci being found. She was immediately put on M and B 693 and improved in 48 hours, her temperature falling and her clinical condition improving. Blood-culture was negative after the first 24 hours. The drug was stopped after 22 grammes had been given.

She was still very ill, and her temperature rose again 24 hours after the drug had been discontinued, so a further 34 grammes
were given, making a total of 50 grammes. At this time, eleven days after admission, she had improved clinically, but the signs in her chest suggested that there was fluid in the pleural cavity. Aspiration was performed on three occasions without finding pus until finally, after her temperature had been irregular for six weeks she began to cough up thick yellow sputum which was almost pure pus. It was decided that she had had an interlobar empyema which had ruptured into a bronchus. From this point she improved and was discharged very well, four months after admission.

Case XVIII was an old man of 74 with auricular fibrillation who was admitted on the 3rd day of his illness with consolidation in his left lower lobe. His sputum contained many type 5 pneumococci, dullness in his chest was so marked that the visiting physician thought that there might be an underlying lung tumour, and so he was not put on M and B 693 for 24 hours.

His temperature fell 48 hours after giving the drug, but his general condition improved more slowly. For the first three nights after admission he was greatly troubled with hiccup, M and B 693 was stopped after he had had 27 grammes.

He did not improve as expected, and his temperature rose again 9 days after admission, while the signs in his chest began to suggest the presence of fluid. Aspiration on two occasions failed to find pus, but a third attempt, 25 days after admission, revealed its presence in the left pleural cavity. It contained many type 5 pneumococci.

Three days later rib resection was done and closed drainage of the pleural cavity instituted. He recovered from the operation, and steadily improved for a fortnight. After that, he began for no apparent reason to lose heart and strength, and went steadily down-
hill, dying of exhaustion three weeks after his operation.

In trying to assess the value of M and B 693 in preventing complications, it is only fair to exclude cases in which absorption of the drug was so poor that it was impossible to maintain an adequate concentration in the blood.

This immediately excludes Case XI who developed an acute otitis media, as he vomited the drug so constantly that its concentration in his blood must have been very low. In any case, his otitis media was synpneumonic, having been present from the beginning of his attack, before the institution of M and B 693 therapy, and therefore could not be ascribed to a failure of the drug.

Case XII is extremely interesting, because the only organism which could be found either in his sputum or his empyema was the pneumobacillus of Friedländer. The role of this organism in acute lobar pneumonia has already been discussed.

Septic complications, especially lung abscess, are very common in Friedländer pneumonia, and in this case M and B 693 failed to prevent the development of an empyema. This does not mean, however, that the drug was without action on the infecting organism. The mere fact that the patient recovered from a disease whose mortality is usually between 80 and 90%, itself suggests that the drug was not ineffective.

The question is more fully discussed later under the heading of the infecting organism.

The remaining two cases of empyema, XVII and XVIII, can fairly be looked on as cases which developed the complication after adequate dosage of the drug.

Case XVII was admitted on the 2nd day of the disease and had no less than 56 grammes of M and B 693, in two courses.
took the drug very well, showing no signs of toxicity, and yet she developed a subsequent interlobar empyema, which did not subside until it ruptured into a bronchus. An interesting feature is that a type 8 pneumococcus was found both in her sputum and blood. No pus could be found in her chest. This organism is one of the types of pneumococci referred to by Whitby in his original article as being especially susceptible to the action of M and B 693. (Whitby 1938)

Case XVIII did not commence treatment with the drug until the 4th day of the disease. He had 27 grammes without any toxic effects being observed, but also eventually developed, an empyema, which had to be treated by open operation, and from which he finally died. The organism found in his sputum and empyema pus was a type 5 pneumococcus. Whitby in the same article, states that this organism is susceptible to the action of M and B 693, but not as strongly so as is type 8.

In these two cases, the only conclusion that can be reached is that M and B 693, given every chance, completely failed to prevent an empyema developing. This would give an incidence of 9%, compared with the 3% found in cases treated without the drug. Although the number of cases is much too small to exclude the effect of coincidence, the fact leads to speculation as to what others have found.

The original impression given by Evans and Gaisford (1936) was that there was a definite increase in the incidence of empyema. They had 6 in their series of 100 cases. Two of these were due to the type 1 pneumococcus, 3 to the Staphylococcus aureus and 1 was sterile. Since then many other workers have
reported series of cases, and the general opinion seems to be that the incidence of empyema is not raised, and is, in fact, lowered, by the use of the drug. The most comprehensive series of cases is the 580 treated in South Africa and reported by Agranat, Dreosti and Ordman (1939). 280 cases were treated with the drug with the development in 3 cases of empyema and in 10 sterile effusions. This is contrasted with 270 control cases in which 4 empyemata, 1 sterile effusion and 2 lung abscesses developed. The cases however do not all rank as normal people, as 115 at Randfontein had been vaccinated against the pneumococcus. In these cases no empyemata developed. However, excluding these cases, the incidence of empyema after drug therapy is only 1% and that of sterile effusions 5%. This last figure is rather higher than is usually found.

Wilson and others, in a review of 30 treated cases and 30 controls, found 1 empyema in the treated cases and 3 in the controls. They also found 12 otitis media and 2 cases of acute mastoiditis in their 30 control cases, as opposed to 5 otitis media in the treated cases. This is an extraordinarily high incidence of septic complications in the untreated series, and suggests that they were dealing with a rather abnormal type of patient.

Meakins and Hanson (1939) treated 30 cases with no empyemmas developing. Anderson (1939) in Nairobi treated 50 cases with 50 controls, with the development of one empyema in the controls and none in the treated series.

On the other hand Graham and others, working in Toronto (1939), had 5 empyemas in 50 treated cases. One of these was pneumoniac and present before treatment began, and so should be excluded. One other died, two cleared up on a continuance of drug therapy and
repeated aspiration, and the other at the time of publication was improving with a similar line of treatment.

The question of the incidence of empyema is thus still sub judice and only time will solve it. Even more interesting, however, than the actual incidence of empyema following the use of M & B 695, is the fact that any pneumococcal empyema can follow a pneumonia adequately treated with the drug, considering the remarkable effects it has on the primary disease. Two cases have been described in my series (XVII and XVIII), the first due to a type 8 pneumococcus and the second to a type 5. Both cases were thoroughly treated with the drug, XVII having 56 grammes in two courses and XVIII 27 grammes, and both took the drug without the slightest difficulty. As has been mentioned before, both of these organisms have been described by Whitby (1938), as being susceptible to the drug, type 8 especially so. Later work, however, (McLean, Rogers and Fleming 1939) has shown that the resistance of the organisms lies in the strain and not the type, which lessens the importance of this. Case XVII developed her empyema a few days after apparent cure of her pneumonia, case XVIII not until over two weeks had elapsed.

In considering possible reasons for the development of these empyemata, it is interesting to note that Graham (1939) in three of his empyema cases, found that the concentration of the drug in the pus, was $2/3^{rd}$s that in the blood. The concentration was not estimated in his two fatal cases. This shows that the drug definitely reaches the pleural cavity in high concentration.

The question was discussed at a meeting of the Royal Society of Medicine reported in the Lancet of the 8th April 1939. Whitby there repeated that the drug exists in the blood partly in an active unchanged form and partly in an
inactive acetylated form. The proportion varied in different people, and perhaps those who acetylated the drug very readily might be those who resisted treatment. Fleming later suggested that certain organisms might develop a resistance to the drug and quoted a case described by Anderson (1939) in which the organism recovered from the patient after death, showed a much high resistance to the drug, than the same organism taken from the patient before treatment began.

It may here be stated that recent experimental work by McLeod and Raddi (1939) has confirmed that pneumococci can become resistant to M and B 693. He grew a type 1 pneumococcus in a medium containing increasing concentrations of the drug, and found that it became highly resistant both in vitro and in vivo. This change was not accompanied by any change in morphology, virulence or specific immunological characteristics.

Banks stated that he and his colleagues had treated 30 lobar pneumonias with a fair proportion of empyemata. In these he found that the concentration of M and B 693 was often higher in the pus than in the blood. He had also often injected the soluble sodium salt into the pleural cavity, and had raised the drug in the pus to a level as high as 100 mg. per 100 c.c.'s. This compares with the usual level in the blood of 7-8 mg. per 100 c.c.'s. (Graham et al. 1939). He suggested that loss of sensitivity of the organism to the drug might have a bearing on the development of empyema.

If it is permissible to put forward a hypothesis, taking my own two cases as a basis, it does seem that the organisms must have developed a considerable resistance to the drug as both seemed to respond to its action to begin with, particularly that present in
case XVlll, and yet later caused the development of empyemata.

It seems possible that in these patients the drug may have been rapidly acetylated, leaving a relatively low concentration of the active form in the blood. This might be sufficient to overcome the organisms in the very highly vascular lung but not those in the less vascular pleura. Although the concentration of the drug may become just as high in empyema pus as in the blood, this need not interfere with the suggestion as, in view of its, poorer vascularity, less of the drug would be in contact with organisms actually in the pleural membrane, as compared with those in the lung tissue itself. This lower concentration of the drug with possibly a high proportion of the acetyl derivative might give those organisms opportunity to become resistant to the action of the drug, and so capable of causing an empyema.

Another possibility, is that relatively resistant strains of pneumococci were being dealt with in the first place and that this interfered with drug therapy. This seems quite probable in Case XVll who had a positive blood culture. Although her temperature slowly fell, reaching 97.5°F 48 hours after the drug was given, her clinical condition did not improve, her white count rose until it was 30,000 5 days after admission, and her pneumonia insensibly merged into an interlobar empyema. This does suggest that the type 8 pneumococcus present was a highly resistant strain.

The other case (XVlll) did not develop an empyema until a week after apparent cure of his pneumonia. His temperature fell to 97°F 48 hours after beginning M and B 693, with marked clinical improvement. From this it would seem that the type 5 pneumococcus present did respond to the drug to begin with. However, in spite of his
normal temperature, his white count did not fall, but slowly rose to between 18,000 and 20,000, remaining there for 5 days before empyema was diagnosed. This suggests that during that period an empyema was insidiously developing, and that the organism, which was not originally highly resistant, had become drug-fast in the pleura.

Since both patients tolerated a high dosage of the drug without any trouble, it may be assumed that an adequate amount was absorbed and a sufficient concentration reached in the infected tissues, but as actual estimations of the drug level in the blood were not made, this remains an assumption. However, as neither showed the slightest sign of intolerance, it seems very unlikely that the resistance of the organism concerned can be ascribed to a poor absorption of the drug exposing it only to a low concentration.

A further possibility for the failure of M and B 693 to prevent empyema is suggested by Lockwood's (1939) observation that the products of protein breakdown, as exemplified by peptone, interfere with the action of sulphanilamide on the streptococcus. Later work by McIntosh and Whitby (1939) has shown that peptone also interferes with the antistreptococcal action of M and B 693, but that it interferes with the action of neither of these drugs against the pneumococcus.

However, as it seems probable that the difference in action on these organisms will only be a matter of detail and not broad principles, it is likely that further investigation will find some other product of protein breakdown which interferes with the action of the drugs on the pneumococcus.

If this is so, an empyema presents just the conditions where products of protein breakdown abound, and the persistence of
organisms, once an empyema has been established, is easily explained. The actual beginning of the empyema may be explained by the suggestions given above (either a low concentration of the drug with a high proportion of the acetyl derivative or a highly resistant strain of pneumococcus) or by the conception that before drug therapy was begun the organism had become established in the pleura, had caused pus formation, and that this had interfered with the drug's action.

If it is true that the products of protein-breakdown interfere with the action of M and B 693, it would be expected that the treatment of established empyema with the drug would meet with little success. This actually does seem to be the general finding in practice.

For example Agranat and others (1939) describe a case, treated with M and B 693, which developed an empyema immediately after a pneumonia which was due to a type 1 pneumococcus. The drug was continued without benefit for 20 days, a total of 65 grammes being given. Finally a rib-resection had to be done.

Once empyema had become established in my case XVII continuance of the drug seemed to be having no beneficial effect, and it was stopped. A further course of drug therapy was not given to case XVIII.

It is only fair, however, to note that opinion is not yet definite on the question, since, as I have already mentioned, (page 108), Graham and others (1939) found that three of their empyema cases cleared up with continuance of M and B 693 and repeated aspiration.

To sum up, I would suggest that the reasons for empyema
developing in cases treated with \textit{M} and \textit{B} 693 may be as follows.

(a) In some cases a high rate of drug acetylation allows the organisms in the pleura to develop a "drug-fastness" and persist in that situation, although they may die out in the lung.

(b) In other cases the pneumococcus present may be of a highly resistant strain.

(c) In yet other cases the organism may become established in the pleura at an early stage in the disease, before the institution of drug therapy, cause pus formation, and so protect itself from the action of the drug.

(d) Finally, the causative organism may not be a pneumococcus, and thus may be insensitive to the drug.

It is of course possible that in any single case several of these factors may be combined.
Serous Meningitis or Meningism.

Under the heading of cases with complications of pneumonia present, Case IV may be discussed.

Case IV This patient was a girl of 15 who was admitted with all the signs of an acute meningitis, and for two days she was so regarded. She came in on the second day of her illness with neck rigidity, head retraction, photophobia, bilateral ptosis and papilloedema, and positive Kernig's and Brudzinski's signs. She was quite irrational and her temperature was 104°F. Nothing abnormal could be found in her chest.

A lumbar puncture was done and the only abnormalities found were that it was under markedly increased pressure and the chlorides were only 678 mg.%. It appeared that the most likely diagnosis was that she was developing an acute tuberculous meningitis. No organisms of any kind could be found in the fluid, and there was no increase in cells.

The day after admission she was worse, and became very violent. The only change in her clinical findings was that her abdominal reflexes disappeared. A further lumbar puncture was done and sent for examination for organisms, but none could be found in a straight film or on culture. There was again no increase in the cell count of the fluid. The white blood count was 26,000.

No sign of a pneumonia could be found in the chest, but it was decided to have a portable X-ray done to exclude the condition. This was carried out the next day, and revealed definite consolidation in the lower part of the left upper lobe. Very careful
examination of the chest then revealed slight dullness below the left scapula with a few fine crepitations but no bronchial breathing. Her sputum contained many type 22 pneumococci.

She was put on full doses of M and B 693 at once, and showed a dramatic improvement, her temperature falling to normal in 24 hours, with great clinical improvement and loss of all signs of meningeal irritation in the same period. She made a rapid recovery without any trouble, apart from a slight frontal headache.

The case is interesting as it demonstrates how intense the signs of meningeal irritation may be, without any actual infective meningitis. It would seem however that she must have had a definite serous meningitis. It is usual to find no abnormality beyond an increase of pressure and perhaps a raised cell count (lymphocytes) in such cases. The low total chlorides found in this case is a very unusual feature and cannot be explained, except, perhaps, on the grounds of laboratory error. The early development of the condition in her pneumonia is also interesting, and suggests that the toxins elaborated by the type 22 pneumococcus which infected her lung entered her blood stream and were there extraordinarily irritant to her meninges.

The details of the case have perhaps little bearing on the action of M and B 693, but it is described because of the comparative rarity of the condition in an adult. It is noteworthy that it cleared up very rapidly when the primary disease in the chest was treated with the drug.

Toxic Effects of the Drug.

Vomiting.

The only serious toxic effect encountered was nausea and vomiting, but this was found to be a very serious obstacle to treat-
ment in certain cases. In an earlier section (page 59), it was stated that the incidence of vomiting seemed to vary greatly in different series of cases, but that the majority found that it was not a serious impediment to treatment, and could usually easily be overcome.

This was certainly not my experience. Six cases vomited during treatment. One (Case XX11) to a moderate degree, two (Cases V111 and 1X) severely, but not to such an extent that treatment had to be stopped, and three (Cases V1, X and X1) so severely that the drug was obviously not being absorbed, and had to be withdrawn. In two of these cases (V1 and X1) the withdrawal of the drug was followed by a spread of the disease in the chest. Case X was fortunately a mild one, and her temperature remained down.

All of the usual methods described for combating vomiting were tried, and all were found useless. The drug was given ground up in milk, flavoured with lemon-juice, sodium bicarbonate was given beforehand, the dose was immediately repeated if vomiting occurred, all without effect. Dilute hydrocyanic acid, chlorbutol and even champagne failed to have any effect.

The injection of the drug, 0.5 grammes suspended in 2.5 c.c's of oil, was tried, but it was found impossible to give a sufficient dosage to obtain a therapeutic effect.

Some workers (Gaisford 1939, Graham et al. 1939) have found that perseverance with the drug stops vomiting. This was very definitely not my experience. Perseverance with the drug usually increased the vomiting, and certainly in no case reduced it. The condition of the three cases who vomited severely (V1, X and X1) was becoming so serious through the exhaustion produced, that the
drug had to be withdrawn. This was followed in all cases by cessation of the vomiting within 24 hours.

From my admittedly small experience the only conclusion that I could draw was that the nausea-producing tendency of the drug was a very serious difficulty in treatment, and that it would be most helpful if some way could be found of eliminating that tendency. The soluble sodium salt for intravenous or intramuscular injection, which has since been produced, might have been the answer to what was a very serious problem.

In my cases the vomiting appeared to be due to a local irritation of the stomach and not to a central action on the vomiting centre, as it usually occurred in the first 24 hours after starting the drug, and occurred immediately after the ingestion of each dose, once it had started. I did not encounter any case in which it developed late in treatment.

Effect on White Cells.

The effect of the drug on the white cells was carefully watched, and the results are interpolated below in the form of a chart.

Chart.

As can be seen, there was no constant effect on the white cells. In most cases the count fell fairly slowly after defervescence. In several cases (Ill, VIIl, X, XIll and XXI) there was a slight rise after the drug began, in three (XI1, X Ill, and XXIll) there was a steady rise over several days and in one case (V) there was a marked rise. This case was admitted almost moribund with a white count of 9,000 and a sedimentation rate of 124 mms. at one
hour (Westergren). Under treatment with the drug she improved dramatically, and her white count progressively rose, with steady clinical improvement until it was 18,000 on the 4th day of treatment. Thereafter it slowly fell to normal.

There was a rise in cases V1 and X1 but these were the cases which vomited severely, and so no significance attaches to it.

In only one case (apart from the moribund case XII1, in which the white cells fell to 1,500 just before death), was there a fall in the white cell count which caused alarm. This occurred in case XVI, where, after 24 hours treatment the temperature fell to normal but the white count also fell to 5800. It was not felt safe to continue with the drug, so it was stopped. Her white count rose to 9,000 and 8,000 on the next two days and to 19,000 on the next day, when her pneumonia recrudesced. She was again treated with the drug, keeping a careful watch on her white count, which did not fall at all rapidly, in spite of prompt clinical improvement. A week after beginning her second course of treatment it was still 12,000 although there was no sign of trouble in the chest. Her convalescence was uninterrupted. From these findings it would seem that the alarm felt in the first instance was groundless, as she obviously had no undue sensitivity to the drug.

These results agree with what is generally found, most workers simply reporting that the drug has no obvious effect upon the white cell count. An occasional case of agranulocytosis, however, has been encountered, as is noted in the section on the toxic effects of the drug. (page 64).
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The figures indicate the white blood count in thousands. 
A gap means that no white count was done. 
Figures in red indicate that the temperature was above 98.4°F. 
Figures in black indicate that the temperature was below 98.4°F. 
An asterisk * indicates that the drug was temporarily stopped. 
A vertical black line "1" indicates the end of drug treatment.
**Methaemoglobinæmia.**

The question of the occurrence of methaemoglobinæmia was not specially studied, the spectroscope not being used. No fewer than 15 cases were cyanosed on admission, cases V, VI, X11, XV11, XIX and XX markedly so. In only one case, however, case XVI, did cyanosis increase under drug treatment. In this case, in spite of a fall of temperature and clinical improvement cyanosis increased and was of a rather slaty colour, and was put down to methaemoglobinæmia. The cyanosis quickly cleared up on withdrawing the drug. In all other cases cyanosed on admission the use of the drug caused a rapid disappearance of cyanosis, concomitant with the improvement in the general condition. As is usual when giving any of the sulphonamide drugs no sulphates or aperients were given during treatment.

No other toxic effects were seen in the twenty-three cases treated.

**The Infecting Organism.**

The series is much too small to draw many conclusions as to the effect of the drug on the various types of pneumococci and other organisms encountered, but it may be interesting to see what they were. Some unusual organisms were encountered, and the effects of drug therapy are compared with the findings of other workers on the same organisms, not necessarily occurring in pneumonia.

**Pneumococcal Cases.**

Fifteen cases were found to have pneumococci either alone or predominating in their sputum. These were typed, and the results were as follows:
Type 1 occurred twice.
" 2 " four times.
" 5 " twice.
" 7 " once.
" 8 " twice.
" 9 " once.
" 22 " once.
" 28 " twice.

It is interesting that although 9 of these 15 cases were due to Group 4 pneumococci several of them were severe, notably cases IV, XI, XVII, XVIII and XX. Both of the cases which developed an empyema had pneumococci of this group in their sputum, case XVII having a type 8 with a positive blood-culture, and case XVIII a type 5, which was also found in his empyema pus. Case XVII had an interlobar empyema which ruptured into a bronchus, and so the organism in the pus could not be identified.

Since the introduction of M and B 693, and the demonstration by McLean, Rogers and Fleming (1939) that the resistance of pneumococci to its action lies in individual strains and not in types, the identification of these may seem rather unnecessary. However, it is believed by many workers that in severe cases the best results are obtained by a combination of drug therapy with the administration of a type – specific antiserum, if one is available, so, in seriously ill patients it would seem advisable that the procedure should be carried out.

It is interesting, too, to know what organism is present simply because scientifically there is much more pleasure in curing
a patient with a type 3 pneumococcus in his sputum, and a heavy blood
infection than one with a less virulent organism in the sputum and an
uninvaded blood-stream.

**Cases in which no pneumococci were found.**

There were 8 cases in which no pneumococci could be found in
the sputum. These can at once be divided into two groups.

(a) Those in which for various reasons it seemed probable
that a pneumococcus was originally present.

(b) Those in which the other organism seemed to be the primary
infecting agent.

Group "a" comprises 3 cases, tabulated below.

**Case 1.** Streptococcus viridans only in sputum.

**Case XXII.** Moderate growth of haemolytic
streptococci and slight growth of
Staphylococcus aureus.

**Case XXIII.** Streptococcus viridans and Staphylococcus
albus in sputum.

In cases 1 and XXIII the sputum was not examined until they had
been under treatment with the drug for 24 hours. As the organisms
present are ordinarily non-pathogenic, it seems probable that
pneumococci were originally present, but had been rapidly destroyed
by the drug.

It is however, well-known that M and B 693 has a marked action
on Streptococcus viridans in subacute bacterial endocarditis, and it
is possible that this organism was the infective agent and was
rapidly overcome. However, the fact that the sputum was not examined
until the drug had been in use for 24 hours invalidates all conclusions.
Case XXI came in on the 3rd day of her illness and had her sputum examined immediately, before being given the drug. A mixed growth of haemolytic streptococcus and a few Staphylococcus aureus was found. Growth of both organisms was scanty especially the staphylococcus, and it seems very probable, in view of this and the fact that the infection was mixed, that a pneumococcus had originally been present, and that these were secondary invaders which had outgrown it. She responded rapidly to drug therapy, suggesting that these organisms may be susceptible to its action.

In the remaining 5 cases, comprising group "b", a pathogenic organism other than a pneumococcus was found in the sputum in pure culture, or in marked predomination, before the institution of drug therapy. I have already discussed the part played by organisms other than the pneumococcus in the causation of acute lobar pneumonia (page 12), and I feel that these cases may fairly be looked upon as examples of non-pneumococcal pneumonias. My reasons I will give below when discussing the cases, which I have tabulated.

Case XII. Only organism in sputum and in subsequent empyema was Friedländer's pneumobacillus.

Case XIII. Staphylococcus aureus and type 2 pneumococcus in sputum.

Case XIV. Staphylococcus aureus alone in sputum.

Case XV. Staphylococcus aureus alone in sputum.

Case XXI. Staphylococcus aureus alone in sputum.

I propose first to deal with the case infected with Friedländer's pneumobacillus, comparing it with other descriptions of pneumonia due to the organism, and reviewing any reports of others who have used M and B 693 against this organism. I will then deal similarly with
the other four cases.

**Friedländer's Pneumonia.**

**Case XII.**

I have already summarised this man's case under the heading of cases which developed empyema (page 99). Friedländer's pneumobacillus was isolated from his sputum in pure culture and in a heavy growth immediately on admission, which was on the 5th day of his illness. It was also later grown in pure culture from the pus of an empyema which he developed. The organism was not typed and blood-culture was negative. He ultimately recovered after surgical drainage.

He seemed to be an undoubted case of a primary Friedländer pneumonia, his signs and symptoms agreeing very closely with those found by Solomon (1937) in his cases. Although his sputum was not examined until the 5th day of his illness the typical nature of the attack, and the fact that the organism was later recovered from an empyema, leaves little doubt that the pneumobacillus was the primary cause.

He was a man of 43, and his illness began with a definite chill. Toxaemia was profound and on admission he was very ill indeed.

His sputum was of the typical nature described by Solomon. It was deeply stained with bright red blood from the second day of his illness. On admission it was profuse, thick and slimy and brightly blood stained. It was quite different from the "rusty" sputum seen in most of the cases due to the pneumococcus.

His temperature was never above 100°F and he had a relative leucopenia his white count being only 8,000 on admission and remaining below 10,000 for four days after admission. Polymorphs
were only 60% on the second day. The highest count reached was 22,000 on one occasion, 9 days after admission.

The signs in his chest were those of an ordinary acute, lobar pneumonia, this observation agreeing rather with Bullowas (1887) observations, rather than Solomon's.

He had a total dosage of 32 grammes of M and B 693, beginning on the day of admission, which he took without any sign of toxicity. His temperature fell to 96°F in 48 hours, but rose again, and 6 days after admission he developed an empyema in which the organism was found in pure culture. He was treated with rib-resection and ultimately made a complete recovery.

In discussing the effectiveness or otherwise of M and B 693 in this case, the first point which emerges is that the patient recovered from a disease whose usual mortality is between 80 and 90%, and has been reported to be as high as 97% in one series. (Solomon 1927). The mere fact of the patient's survival suggests that the drug was not without action.

His temperature fell 48 hours after beginning the drug but rapidly rose again. As an intermittent temperature is a typical feature of this type of pneumonia, this initial fall cannot in itself be taken to indicate that the drug was effective, but concurrently with it there was a very marked clinical improvement, which lasted until the development of his empyema. This does suggest that the drug had a considerable action in combating his infection.

The fact that he developed an empyema must be admitted as an argument weighing against the effectiveness of the drug, but it is by no means a conclusive one. Empyemas, as I have already remarked, are by no means rare in cases of pneumococcal pneumonia in which the
primary infection has responded well to the drug. Two of my own cases demonstrate this (XVII and XVIII). The mere fact that an empyema developed cannot therefore be taken to mean that the drug was inactive.

It is well-known that the Friedländer pneumobacillus has a marked tendency to cause suppuration in cases which survive long enough. Solomon, for instance, encountered 6 cases of gross lung necrosis and 2 empyemas in his 32 cases (1937). Therefore it seems quite a reasonable statement to say that in my case the drug kept him alive, and so allowed him to develop an empyema.

The case did not come under treatment until the 5th day, and so it seems very possible that an organism with such pus-forming propensities should have already established itself in the pleura and surrounded itself with necrotic tissue products which protected it from the action of the drug. Presumably necrosis had not yet taken place in the lung-tissue.

It seems to me that in view of the survival of the patient and the marked clinical improvement that occurred, M and B 693 may be said to have had a considerable effect against the Friedländer pneumobacillus in this case. It is not, of course, possible to generalise from one case, but the result obtained suggests a search of the literature for other workers' results with the organism.

The condition is so rare that I have not been able to trace any other detailed reports of the treatment of a case of acute Friedländer pneumonia with M and B 693, but some experimental work has been done, and there is a full report of a case of septicaemia due to the organism, with the portal of entry unknown, treated with the drug.
I shall begin by discussing the experimental work, including that where the earlier sulphonamides were used.

**Experimental Work.**

The first report is that of Levaditi and Vaisman (1935a). They used rubiazol 1, which, as I have already remarked, is the same as prontosil red. They found that this drug had no therapeutic effect upon experimental Friedländer's infections.

Burgers (1937) using prontosil red, came to the same conclusion.

Buttle and others (1937) found that sulphanilamide gave some degree of protection in mice infected with the organism. Gross, Cooper and Lewis however also using sulphanilamide, found that it was quite ineffective. (1938).

Recently Bliss and others, using sulphanilamide and M and B 693, found that both drugs delayed death in mice given one minimum lethal dose of Friedländer's pneumobacillus, M and B 693 being markedly more effective. (1939).

The position at present in experimental work is summed up by Long and Bliss (1939 b), who say that, using sulphanilamide, their results agree with those of Buttle, quoted above. They go on to say that if M and B 693 is used as the therapeutic agent, the results obtained in the treatment of experimental Friedländer's bacillus infections in mice are very good, better in their experience than those obtained when the drug is used in experimental pneumococcal infections.

**Clinical Results with M. and B 693.**

Plummer and Ensworth (1939) report a case which showed
Friedländer's pneumobacillus in the sputum along with aerobic and anaerobic organisms. The patient died, but obviously the case bears no relation to the pure Friedländer bacillus infections I have been discussing, and provides no test of the efficacy of the drug.

Agranat and others (1939) mention in their table of bacteriological analysis two treated cases of the infection and two controls. No further details are given, and, in view of the fact that all four recovered, it seems rather doubtful if they were real Friedländer pneumonias.

The best report of a Friedländer pneumobacillus infection treated with M and B 693 is that of Mayer and Antman (1939). This was a case of septicaemia due to the organism, the portal of entry being unknown. He was given 57 grammes of the drug in 12 days, and his temperature became normal 48 hours after it was begun. Blood-culture was almost negative by the time the temperature fell. He made a complete recovery, without any sign of complications, and was very well at the time of publication, 5 months after his illness.

Long and Bliss (1939b) mention that their employment of M and B 693 in pneumonia due to the Friedländer bacillus was at the time of publication limited to one case. Although a heavy bacteraemia was reduced practically to nil, the patient succumbed.

However their view is that because of the beneficial effect of this compound in experimental infections in mice, it should be used in all types of Friedländer bacillus infections in human beings.

My single case, although not of much value taken by itself, at least helps to support this contention.
Staphylococcal Pneumonia.

I now propose to summarise the four cases in my series in which the Staphylococcus aureus found alone or in marked predomination in the sputum, and then to discuss the part played by this organism in their illness, and the way in which it responded to M and B 693.

Case-Histories.

Case X111.

This case has already been summarised under the heading of fatal cases. (page 91).

She had a right lower lobe pneumonia, and died 9 hours after admission, on the 4th day of her illness, apparently from pulmonary oedema.

In her sputum which was thick and yellow, many staphylococci of the aureus type were found and also a few type 2 pneumococci. The staphylococci markedly predominated in a film of the sputum, and culture gave a pure growth of Staphylococcus aureus. Blood-culture was not done. In the University specimen of sputum only staphylococci were found.

An interesting feature of her case was that just before death her white blood count fell to 1,500.

She had only 4 grammes of M and B 693.

Case XIV.

This was a man of 52, who came in on the 5th day of his illness with a right upper lobe pneumonia. He was very ill indeed, with a temperature of 102°F and a white blood count of 24,300.

His sputum had never been rusty, and was now thick and yellow. A straight film showed only staphylococci and culture gave a pure
growth of *Staphylococcus aureus*.

He was put immediately on full doses of M and B 693 and improved dramatically, his temperature falling to 97°F in 48 hours with very marked clinical improvement. He continued to improve and was discharged in excellent health 25 days after admission.

A curious finding was that 8 days after admission his sputum still gave a scanty growth of *Staphylococcus aureus*. At that time he was feeling very well, his temperature was 97°F, his white count below 10,000 and the only sign left in his chest was slight dullness on percussion over the right upper lobe. An X-Ray taken 3 days later showed that the chest was practically clear.

Blood-culture was not done in this case. He had a total dosage of 19 grammes of M and B 693 in a period of 4 days.

**Case XV**

This patient was an old man of 70, who was admitted on the 5th day of his pneumonia, with a right middle-lobe consolidation.

He was extremely ill, being collapsed, delirious and slightly cyanotic. His temperature was 101°F and his white count 20,700.

As with the previous case his sputum had never been rusty. It was thick and yellow and copious. Only staphylococci could be seen in a film, and culture gave a pure growth of *Staphylococcus aureus*. Blood-culture was negative.

He was immediately put on M and B 693. His temperature fell to 98.4°F in 24 hours, rapidly rose again to 100.5°F and then again rapidly fell, reaching 97°F 48 hours after admission. Clinical improvement was not as rapid. He was delirious for his first three nights in hospital, but improved greatly on his 4th day.

He then made steady progress, although his white count
remained rather high, not reaching 10,000 until 8 days after admission. On the 12th day his temperature rose for some unexplained reason to 101°F and his white blood count to 22,300. No signs of an exacerbation could be found in his chest, or of any trouble anywhere else, and he did not feel ill. An X-ray of his chest showed considerable resolution in his right middle lobe, and no sign of any extension of his disease.

His temperature fell within 24 hours, and he showed no signs of further trouble, being discharged very well 36 days after admission. An X-ray of the chest taken shortly before discharge showed complete resolution.

The total dosage of M and B 693 was 30 grammes, given in a period of 6 days.

Case XXI.

This was the youngest case in my series, being a boy aged 10 years. He had a right middle lobe pneumonia. He was very collapsed and was slightly delirious. His temperature was only 98.4°F, but his white blood-count was 21,000.

His sputum had never been rusty and on admission was copious, frothy and yellowish. In a film only staphylococci could be seen, and on culture a pure growth of Staphylococcus aureus was obtained. Blood-culture was negative.

He came in during the evening, and, in view of his low temperature, he was only given a sedative and his progress watched.

The next morning his temperature had risen to 103.5°F and he was very ill indeed, being collapsed and intensely toxaemic. His white-count was 22,000. M and B 693 was therefore started in the
morning, with an initial dose of 2 tablets, in view of his age. This dosage was continued four-hourly.

Blood-culture was repeated and a Staphylococcus albus was found. This may have been a contaminant but may have been a white variant of the Staphylococcus aureus. Unfortunately virulence tests were not carried out, so the question cannot be settled.

He responded very well to the drug, his temperature falling to 97° in 48 hours. At this time he was still delirious and very collapsed, but improved rapidly, his clinical condition being much better 72 hours after beginning the drug.

Blood-culture was negative on the third day after admission. The blood was taken off after his temperature had fallen.

His white count had fallen to 10,000 four days after admission, and did not rise again. He continued to improve, and was discharged 23 days after admission, without any sign of further trouble.

He had 19 grammes of M and B 693 in a period of 4 days.

Discussion.

The first thing that I should point out is that the bacteriological findings in these cases do not rest on the results of a single examination. All of them were done by myself and checked by the Bacteriology Department of the University of Edinburgh. This confirms the fact that the Staphylococcus aureus really was alone or predominating in the sputum, and was not simply a chance finding on an isolated occasion.

The white staphylococcus found in the blood of case X1I was in one of the University Specimens. My own were sterile.

I shall begin by discussing case X111, which differs from the
others in several respects, the main one being that she had a mixed infection in her sputum both a Staphylococcus aureus and a type 2 pneumococcus being present. Her sputum too, was rusty at the beginning of her illness unlike the other 3 cases.

These facts make it possible that she began with a pneumococcal acute lobar pneumonia, due to the type 2 pneumococcus, and that the Staphylococcus aureus was a secondary and fatal invader.

However, certain other considerations would seem to suggest that the staphylococcus may have been the primary organism.

Firstly, she was admitted fairly early in the course of her pneumonia, coming in on her 4th day. This hardly seems to give the staphylococcus time to oust the pneumococcus so completely from its hold on the patient.

Secondly, the only pneumococci which were seen were a very few in a straight film of the sputum. The staphylococcus was overwhelmingly predominant, and culture of the sputum gave a pure growth of Staphylococcus aureus. Furthermore the pneumococci were only seen in my specimen, the University only finding staphylococci.

Thirdly, her pneumonia did not run the usual course of even a severe pneumococcal pneumonia. Her rapid death and white count of only 1,500 suggested an overwhelming toxaemia.

The balance of probability, it seems to me, suggests that the staphylococcus was the primary infecting organism, and that the few pneumococci present, were mouth contaminants. The fact that they were only found in one specimen seems to me especially to support this view. However, even if the pneumococcus did play
some part at the beginning, the Staphylococcus aureus was so markedly predominant at the time of admission, that it seems to me justifiable to call her condition "acute staphylococcal pneumonia" in any case.

As she died 9 hours after admission and only had 4 grammes of M and B 693, she obviously provides no test of the drug's action, and her case is only included in my series because of the interesting and unusual bacteriological findings, and the interesting comparison with the other staphylococcal cases.

The other 3 cases are a simpler proposition in that only the Staphylococcus aureus could be found in their sputum at the time of admission. This finding, in my opinion, means that, whether the staphylococcus was the primary invading organism or not, it was the infecting organism at the time of admission, and the condition could justly be regarded as "staphylococcal pneumonia." Treatment had to be directed at the Staphylococcus aureus which was present and not at a hypothetical pneumococcus which might have been present earlier in the illness. This view is strongly supported by Finland (1934) who points out that in pneumococcal pneumonias consecutive infection with other organisms certainly occurs, and that this secondary infection may defeat specific measures directed at the primary pneumococcus.

He quotes a case of acute lobar pneumonia, which is very much to the point in this discussion, where a type 1 pneumococcus was found in the sputum early in the disease. He does not say whether staphylococci were also present. Specific serum was given without benefit, and the sputum became purulent. The patient died
18 days after admission, and a post-mortem was done. The whole of
the right lung was consolidated, and contained many large abscesses.
The pus from these abscesses from the consolidated lung and from
abscesses which he had in his parotid glands, all yielded a pure
growth of Staphylococcus aureus. No pneumococci could be found.

This case seems to have been a definite example of a
consecutive staphylococcal infection which proved fatal to the
patient, while the original pneumococcal infection was cured by
specific antiserum. It would be interesting to know if
staphylococci were originally present in the sputum however, as
the case may have been staphylococcal from the start, the
pneumococci merely being mouth-contaminants.

In any case, the example proves my point that, whatever the
original infecting organism, treatment must be directed at the
one found at the time of admission, and therapeutic results
obtained should be considered to be effects obtained against that
organism.

In my three cases, at the time of admission, only the
Staphylococcus aureus could be found in the sputum, in a straight
film and on culture. It therefore seems to me that whether this
organism be regarded as primary or not, it was the infecting
organism at the time of admission, the cases may be described as
"staphylococcal pneumonias," and the results of M and P 693 therapy
may be regarded as having been obtained against the Staphylococcus
aureus.

It is my view, however, that in these cases the staphylococcus
may have been the primary infecting organism, and I propose to give
my reasons for this.
In the first place, if a pneumococcus was originally present, it is remarkable that it should have been displaced so completely that in all three cases only staphylococci could be seen in a film of the sputum, and a pure culture of the organism was obtained. It would seem reasonable to expect some signs of a mixed infection. The cases were not admitted early in the disease, XIV coming in on the 5th day, XV on the 5th day and XXI on the 4th, but even so, it seems peculiar that no pneumococci could be found if they were the original cause of the disease.

Secondly, in all of these cases the sputum differed from the beginning from that usually seen in a pneumococcal pneumonia. The patients all stated that it had been yellow from the start. Rusty staining had been entirely absent. It is interesting to note that in Finland's case quoted above, in which he believes there was a primary pneumococcal infection, the sputum was rusty at the beginning of the disease, and later became yellow and purulent. He implies that it was at this point that the secondary staphylococcal infection took place. In my cases the sputum was yellow from the start, suggesting that the staphylococcus was originally present.

In the third place all of these cases were very toxaemic and collapsed on admission, two of them being delirious. Although in itself this fact is not of much significance, it helps to support the idea that something beyond a simple pneumococcal infection was active in these cases.

Fourthly, although these cases responded to M and B 693 in a way which I shall discuss below, the response was slower than was the case with my pneumococcal pneumonias, suggesting that some other
more resistant organism was present.

The main reasons for hesitating to regard these cases as primary staphylococcal pneumonias is (a) the mildness of the infection, in that there was no sign of abscess formation and all 3 cases recovered and (b) the unlikelihood of seeing so many cases of such a rare condition in so short a space of time.

(a) Mildness of infection.

Let me first deal with the question of abscess formation. It is well-known that this is common in staphylococcal infection anywhere, and particularly in the lung. I should suggest that its absence in these cases may have been due to 3 factors.

(1) The staphylococci in these cases may have been of a lower virulence than is usually found in this disease. They were certainly of a lower virulence than the staphylococcus that was so rapidly lethal in case XVIII.

This is rendered more probable by the fact that there was only 1 doubtful positive blood-culture (Case XXI).

(2) The cases came in on the 4th and 5th days of their illness, as I have already noted, and it seems possible that tissue-breakdown might not have proceeded very far in that time, in the absence of a highly virulent organism.

(3) The further progress of tissue-breakdown was probably prevented by the apparently powerful action of M and B 693 on the organisms present.

(1) Low mortality.

I should suggest that this probably depended on 2 factors.

(1) The suggested relatively low virulence of the infecting staphylococcus in the 3 non-fatal cases.
(2) The apparently highly effective antistaphylococcal action of the drug which was used.

(b) Rarity of Infection.

I have already pointed out that staphylococcal pneumonia is apparently very rare, Cecil (1927) finding the organism in only 0.1% of his cases and Bullowa (1938) in 0.7%. However, it has been suggested (Chickering/1919) that the infection is epidemic, at least in the broncho-pneumonic form. If this is so, there seems little reason why this should not be the case in a lobar type of infection.

This suggestion receives considerable support from the experience of Agnes Maegregor (1936) which I have already quoted in some detail (page 31). She encountered no fewer than 10 staphylococcal pneumonias, of which 6 were lobar, in a period of 9 months in Edinburgh in 1935-36. She suggests that in that period the staphylococcus in Edinburgh was in a state of increased virulence, and that she was dealing with an epidemic.

All of her cases were fatal examples of the disease which had come to the post-mortem room, and the diagnosis of "staphylococcal pneumonia" was only made after death. It seems quite possible that many milder examples of the disease may have gone unrecognised, been treated as ordinary pneumococcal pneumonias, and have recovered.

It seems possible that I may have encountered a similar epidemic in the same city in 1939, but that in this case the staphylococcus was not of quite such a high virulence. Three of my cases (XIII, XIV and XV) began within 2 days of one another (2 on the 6th of January and 1 on the 8th) and the other a month later (7th of February), a finding which supports my suggestion.

It is my belief that, in spite of the rarity of the infection
in large series of cases, these four cases were examples of true
primary staphylococcal pneumonias, occurring in a presumably
localised epidemic. In none of the cases was there any sign of
a primary staphylococcal focus outside the lung.

Effects of Drug Therapy.

It remains to discuss the effects of M and B 693 on these
cases, and the results were extremely interesting. I have given
my reasons for believing that these results should be regarded
as having been obtained against the Staphylococcus aureus, whether
it is considered to be the primary infecting organism or not.

As I have already mentioned, Case X111, which died 9 hours
after admission and had only 4 grammes of M and B 693, cannot be
regarded as having provided any test of the action of the drug,
and must be excluded from a consideration of results gained.

The other 3 cases all showed an excellent response to the
drug, the symptoms and signs subsiding rapidly, though not as
rapidly as in my pneumococcal pneumonias.

Case XIV had a normal temperature in 48 hours, and a marked
clinical improvement in the same period.

Cases XV and XXI both had normal temperatures in 48 hours,
but clinical improvement was slower, not being marked until 72
hours.

It can be seen that, as with pneumococcal pneumonias, clinical
improvement tends to occur about 24 hours after the temperature
has fallen.

The rather slower initial response of the temperature to the
drug suggests that the staphylococcus is more resistant to the
action of M and B 693 than is the pneumococcus.
Conclusions.

Although it is impossible to generalise from 3 cases, my strong impression was that M and B 693 was highly active against the Staphylococcus aureus, although not as highly as against the pneumococcus. The fact that all three cases responded strongly supports this suggestion.

M and B 693 and the Staphylococcus Aureus.

The apparently striking results which I obtained in my 3 staphylococcal cases suggests a search of the literature to see what other workers have found with regard to the action of the drug on the organism.

I shall begin with experimental work, and shall then go on to clinical results.

Experimental Work.

A. In Vitro.

The first experiments carried out were most discouraging. Long and Bliss (1938 b) found that neither sulphanilamide nor M and B 693 had any action on the staphylococcus in broth culture. Britton (1938) also came to the conclusion that M and B 693 was almost useless against the staphylococcus. He obtained effects only with concentrations of the drug impossible of attainment in the human body, and with an inoculum of 2,000 organisms could get no results at all in human blood.

Maegraith and Volum (1938), trying out sulphanilamide, soluseptasine and M and B 693, found that none of these drugs had any effect against the organism, using deleucocyted and defibrinated blood as media.
It is known of course that while the "in Vitro" testing of the activity of a chemotherapeutic agent is of interest and value the results do not run parallel with the results obtained "in Vivo" so that whenever an animal is available which is susceptible to infection by the organism the more laborious method of animal assessment has to be used.

B. In vivo.

Fortunately experiments in vivo have been much more successful, suggesting that the drug has at least some effect on the organism. It is very difficult to give a mouse a staphylococcal septicaemia, because, as in man, the organism is not highly invasive and tends to form local abscesses. However, these difficulties have been overcome, and several reports on the results of M and B 693 therapy on such infections in mice, have appeared.

Whitby (1938 b) and Mayer (1938), both using intra peritoneal inoculation of Staphylococcus aureus in mice, have reported a fair degree of success. Whitby found M and B 693, distinctly more successful than sulphanilamide in such infections, but had several late deaths, two mice dying six days after treatment had stopped, two more two days later, and one on the following day. Mayer cured most of the mice that he infected with Staphylococci, compared with a survival rate of only 50% when using sulphanilamide.

Browning (1939), trying out M and B 693, rodilone (pp diacetyl diamino diphenyl sulphone) and pp monoacetyl diamino diphenyl sulphone, found that although the effects of these drugs against Staphylococcus aureus were not striking, they were all more effective than sulphanilamide.

Recently Powell and Chen (1939) have reported that M and B 693
has a curative effect on Staphylococcus aureus infections in mice, as opposed to the effect of sulphanilamide, which they found frequently prolonged life, but seldom saved it.

Long and Bliss (1939) have also studied the question, using a method of intravenous injection of large numbers of staphylococci in mice, instead of intraperitoneal inoculation. They found that at the end of the first week of treatment with M and B 693 73% of the mice were alive, as compared with 34% of those treated with sulphanilamide. All the control mice were dead by the 6th day. At the end of the second week, four days after stopping the drugs, 33% of the mice treated with M and B 693 were alive, while only 8% of those treated with sulphanilamide survived. They suggest that the effect of M and B 693 on staphylococcal infections in mice is definite enough to warrant careful clinical trial in human infections. They recommend that a high blood concentration, in the neighbourhood of 10 mgs.%, should be aimed at, and mention that they have already had dramatic results in two severe staphylococcal infections in human beings. In a later publication (1939 b) they state that M and B 693 is more effective in the control of staphylococcal sepsis, than any other chemotherapeutic compound which they had tested so far.

The last statement may be taken to sum up the present position in the experimental world, but any drug stands or falls by the results found in clinical practice. So far, a large number of case reports has not been published, and no large series has appeared, analogous to that of Evans and Gaisford with the pneumococcus, for the obvious reason that severe staphylococcal infections are relatively uncommon. However clinical reports are accumulating that the drug is
of great value in such infections.

**Clinical Results.**

The first report of successful treatment of a staphylococcal septicaemia with M and B 693 was that of Fenton and Hodgkiss (1938). Their case resulted from the incision of an infected arm, and was due to a *Staphylococcus aureus*. The drug had a most dramatic effect, the temperature being subnormal within 24 hours, and there was no sign of further trouble. A total dosage of 27.5 grammes was given, spread over a period of 14 days.

The next case was that of Maxwell (1938), whose patient had a staphylococcal pneumonia in the left upper lobe, with a positive blood-culture of *Staphylococcus aureus*. There was a rapid response to M and B 693, the temperature falling to normal within 48 hours. A total dosage of 23 grammes was given in the space of 4 days. A curious fact was that the blood-culture was still positive 4 days after the temperature had fallen. It then remained negative and convalescence was rapid, without any sign of further trouble.

The only other reference to the treatment of staphylococcal pneumonia that I have been able to find is by Long and Bliss (1939 b) who state that they have used M and B 693 in a few cases and found it quite effective. In one patient with an involvement of the left lower lobe and a staphylococcal bacteraemia, administration of the drug was followed by a critical fall of temperature, sterilisation of the blood, and rapid resolution of the pneumonia.

O'Brien and McCarthy (1938) report the treatment of a case of *Staphylococcus aureus* septicaemia following a whitlow and boils. Sulphanilamide and prontosil soluble had failed, but M and B 693
was dramatically successful. A total dosage of 22.5 grammes was
given in 17 days.

Goldberg and Sachs (1939) describe 2 cases of osteomyelitis
with positive blood cultures of Staphylococcus aureus treated with
M and B 693. The first case was treated with sulphanilamide, which
failed to have any effect, the blood culture remaining positive.
After 5 days of M and B 693 therapy the blood became negative, but
the temperature was not normal until the 11th day, 43 grammes of
the drug were given in a period of 16 days.

The second case was treated with M and B 693 from the start,
and the blood became negative after 4 days. The temperature was
normal in 7, and the drug was stopped on the 10th day when 62
grammes had been given. On the 13th day the temperature rose again
and the drug was recommenced and the temperature rapidly fell, with
clinical improvement. Eighteen grammes were given in 3 days.

They believe that M and B 693 sterilised the blood-stream and
that this points to a specific action on the staphylococcus,
suggesting trial in a large group of cases.

Wade (1939) reports a case of Staphylococcus aureus septicaemia
which was first treated with Uleron, 15 grammes were given in 5 days
but the patient's general condition deteriorated to such an extent
that a blood-transfusion was necessary. Blood-culture was still
positive, so it was decided that the drug was having no effect and
it was stopped.

He became steadily weaker, and after a lapse of 4 days, M and
B 693 was administered in the hope that it might do some good. His
temperature rapidly fell and remained normal for 7 days. Blood-
culture immediately became negative and remained so, 30 grammes of
the drug were given in 8 days, after which it was withdrawn.

Four days later his temperature rose again and his bloodculture again became positive. A further 36 grammes of the drug were given during the next 12 days, with immediate improvement the blood-culture again rapidly becoming negative. Since then he has had no further trouble, and has made a complete recovery.

This case is described in some detail because of the very interesting comparison between Uleron and M and B 693. The former drug which is widely used on the continent, and to a fair extent in this country in severe staphylococcal infections, was apparently quite ineffectual while the latter had an immediate beneficial effect.

McConney (1939) describes the successful treatment of a similar septicaemia following on multiple boils of the face and neck. The temperature fell in 48 hours with rapid recovery. Seventy three grammes were given.

Galewski and Stamma (1939) report a case of staphylococcus albus septicaemia which reacted well to M and B 693. Forty two grammes were given in a period of 7 days. The blood was sterile on the 4th day and the temperature was then 99°F. The pathogenicity of this organism must be in considerable doubt, especially as no tests of virulence were carried out.

The most recent report I have found is that of Abramson and Flacks (1939). They describe a series of six cases of staphylococcal septicaemia. The first 4 were aureus infections, were treated without M and B 693 and all died. The last 2 were treated with M and B 693 and both recovered. One was an aureus infection, and the other
an albus. Again no tests of virulence were carried out on this latter organism.

The aureus case had 118 gms. and the albus 72. All of the cases were of severe boils or carbuncles of the face and the last two successful ones were treated in addition to drug therapy, by immediate tying of the angular vein. This was not done in the other cases.

This series of successful cases surely suggests that the drug must have a fairly high degree of antistaphylococcal action considering that the usual mortality from staphylococcal septicaemia is 66 - 90%. It is interesting to contrast the current views taken by the two leading medical journals in this country. The British Medical Journal of October 28th (1939), makes the cautious and rather pessimistic statement that staphylococcal infections seem likely to resist chemotherapy, and leaves it at that. The Lancet of November 18th (1939), on the other hand states that while isolated instances of cure apparently effected by a particular treatment may not mean much, the clinical evidence now accumulating about the benefit of chemotherapy in staphylococcal septicaemia encourages a more optimistic prognosis. It also suggests that when a Staphylococcus albus is encountered its pathogenicity should be established by the coagulase test of Cruickshank (1937).

That the effective chemotherapy of Staphylococcal infections by this type of compound will be possible seems supported by the discovery that a compound analogous in structure to M and B 693 but containing a methylthiazole in place of the basic pyridine group has an activity against the Staphylococcus. Both in vitro and in experimentally infected mice as well as clinically. (Herrell and
Brown (1939) the preliminary results suggest that this compound may be more active in Staphylococcal infections than M and B 693 as well as less likely to produce vomiting, these results await confirmation however.
Conclusions.

(1) The treatment of 23 cases of acute lobar pneumonia with M and B 693 is described. There were 3 deaths, none of which can be ascribed to a failure of drug action. No controls were available, but this result compares very favourably with the usual mortality of the disease.

(2) The drug had a striking effect on the temperature, which in most cases was reduced to normal within 24 hours. Clinical improvement was rather slower, occurring usually in 48 hours.

(3) There appeared to be no effect on the rate of resolution of the signs in the chest, which disappeared at about the same time as would have been expected in cases treated without the drug. There were no cases of delayed resolution.

(4) The drug did not seem to be effective in preventing the onset of complications, as 3 cases developed an empyema. However, the small number of patients involved does not exclude the effect of coincidence.

No sterile effusions were encountered.

(5) A case of so-called Friedländer pneumonia is described. The drug seemed to have a considerable action against the pneumobacillus, although it did not prevent the development of an empyema. The patient survived.

(6) Four cases of "staphylococcal pneumonia" were encountered. One was moribund on admission and rapidly died, but the others showed a good response to the drug.

M and B 693 therefore appeared to possess a powerful anti-
staphylococcal action.

(7) One case had a mixed growth of haemolytic streptococcus and Staphylococcus aureus in his sputum. There was a prompt response to the drug.

This helped to confirm the anti-staphylococcal action of M and B 693, and also suggested that it was active against the haemolytic streptococcus.

(8) The only serious toxic effect encountered was the fairly frequent occurrence of vomiting, which in some cases was a serious impediment to the use of the drug. No way of overcoming this difficulty was discovered, short of withdrawing the drug.

The drug did not seem to have any toxic action on the white blood cells.

(9) The final conclusion reached was that M and B 693 is an extremely effective agent in the treatment of acute pneumococcal or staphylococcal lobar pneumonia, and that it may be of considerable value in the treatment of Friedlander pneumonia.
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