

THE SULPHANILAMIDES IN GONORRHOEA

Thesis submitted for the

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by

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THE SULPHANILAMIDES IN GONORRHOEA

Introduction.

It is difficult to realise that in four years the treatment of gonorrhoea has been revolutionised by the introduction of the sulphanilamides. Previous to this the results obtained were by no means good even in expert hands, despite an Act of Parliament being passed which prohibited treatment except by qualified practitioners. Complications were many, and certain cure by no means universal. But in 1936 Professor Domagk claimed to have discovered a substance, a dark red dye, which had a specific action against streptococci, and which he called Prontosil. Further investigations confirmed his findings. This was a notable discovery. It is true that even in the 17th century quinine was known to be effective in malaria, and from early days mercury was used in syphilis. In 1910 Ehrlich and Hata had discovered a synthetic organic arsenical, Arsphenamine, later Neoarsphenamine, and had proved its clinical value in spirochaetal infections. Thus, though it had been recognised that protozoal infections could be treated by chemotherapy, bacterial diseases were still thought to be resistant to this type of therapy, and any drug which would kill/

kill bacteria was thought to be too toxic for the host.

Subsequent to the discovery of Prontosil, chemists in all countries have attempted to improve on it, and we in this country have used sulphanilamide, sulphapyridine, and now sulphathiazole. Venereologists soon realised that here they had a drug which could be taken by the mouth for the cure of gonorrhoea, and this has opened up a tremendous field for investigation which is still going on. There is much to be done to find the correct dosage and time to give it, and how to avoid toxic effects, and many other points are still under review.

The figures published by the Chief Medical Officer of the Ministry of Health show that in 1938 there were 41,759 cases being treated in treatment centres in England and Wales, and in 1937, 43,802, of which 29,250 were new cases and over 27,000 of less than one year's duration. Of these, 21% of males were defaulters, i.e. not having been discharged as cured or not having completed treatment. The fall of over 2,000 is no doubt due to the sulphanilamides. When it is realised what a toll is taken on the health of the community by gonorrhoea alone, it is apparent that if we have a drug of the sulphanilamide group which will cure early and certainly, we are making a great advance. It is of even/

even greater importance in these days when the whole country is working at top pressure if a man can be cured early, and without delaying complication go back to his working bench in the minimum period of time. Even now the Minister of Health reports an increase of 15% in venereal disease which is almost always the case in time of war.

If we consider also the Armed Forces and look at the following tables for 1937, we realise how gonorrhoea affects their efficiency, especially now when we are calling up so many men. Every man who is found to be suffering from gonorrhoea has to go to a special hospital for two weeks and remain under observation for three months, and if the sulphanilamides can shorten this time they will be of extraordinary value.

Table 1

Admission to Hospital per 1,000 for 1937 for acute gonorrhoea in the Royal Navy Home and Abroad.

<u>Stations</u>	<u>Average Strength</u>	<u>Acute Gonorrhoea</u>
Home	34,160	17.97
Home Fleet	14,735	21.85
Mediterranean	22,700	32.11
N.American W.Indies	2,245	81.06
China	8,190	114.16
East Indies	3,260	28.83
Africa	1,110	92.88

Table 2

Royal Air Force.

<u>Stations</u>	<u>Average Strength</u>	<u>Gonorrhoea</u>
Home	35,823	4.1
Abroad	12,011	12.1

Table 3

The Army.

<u>Stations</u>	<u>Average Strength</u>	<u>Gonorrhoea</u>
Home	89,605	8.2
India	59,059	25.7
Aden	380	15.8
Bermuda	437	36.3
Ceylon	273	84.2
North China	-	-
South China	5,960	105.0
Shanghai	-	-
Egypt	15,840	24.5
Gibraltar	2,006	16.5
Jamaica	539	61.2
Malaya	3,270	37.0
Malta	4,131	11.9
Mauritius	115	113.0

In the present thesis the author proposes to describe the results of treatment by the sulphanilamides in a series of 180 cases. These cases were treated/

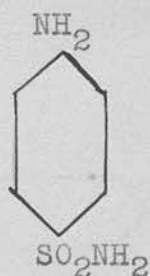
treated at the Venereal Diseases Clinic of the Cumberland County Council and Corporation of Carlisle at the Cumberland Infirmary. Patients were drawn from Carlisle, Cumberland, adjacent parts of Scotland, and Westmorland.

Chemistry and Pharmacology of the Sulphanilamides

From a chemical point of view the compounds of sulphanilamide are divided into two classes, the first where there is a substitution of the amino group, and the second where there is a substitution of the amide group.

Figure 1

Sulphanilamide.



Amino group
(Class 1 substituents)

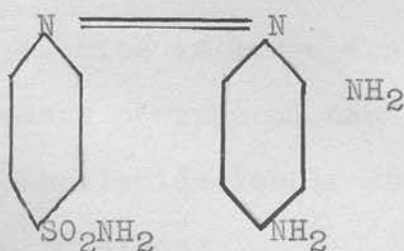
Amide group
(Class 2 substituents)

In the first class (fig. 1) we have the original Prontosil which is now used more on the Continent. Chemists working not only in this country but in France and America have shown that this compound owed its activity to reducing in the body to active sulphanilamide and inactive triamenobenzene.

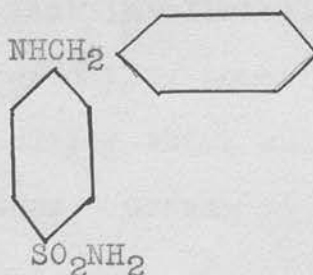
Figure 2

Compounds of Sulphanilamide.

Prontosil



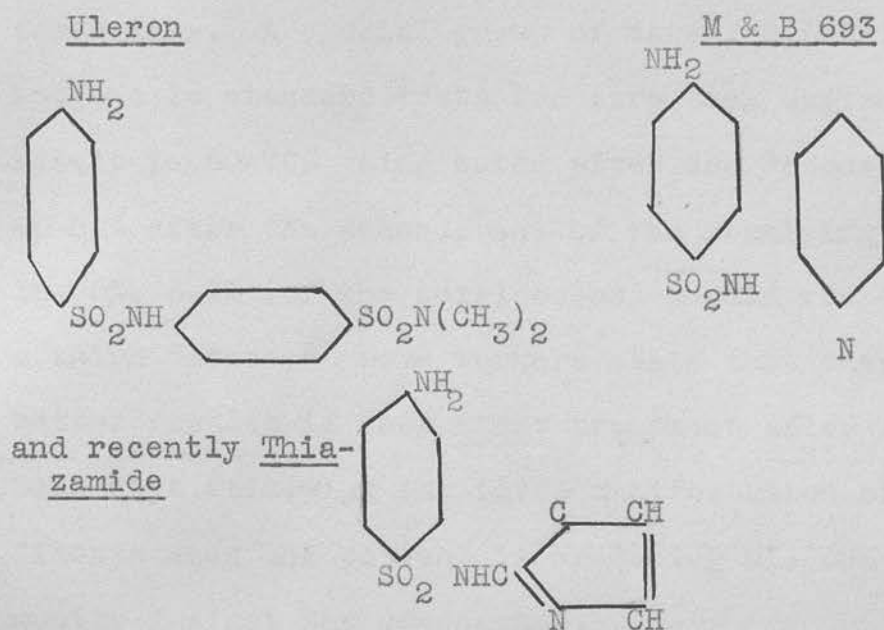
Proseptasine



Compounds in the second class (fig. 3) do not split up into sulphanilamide in the body. The two substances of this body which have been used are Uleron and M & B 693.

Figure 3

Compounds of Sulphanilamide.
Class 2 (substituents of amide group)



The two compounds now most widely used in gonorrhoea are M & B 693 and Uleron, the former in this country and the latter abroad, especially in Germany. As regards Uleron, since 1937 it has been estimated that over half a million cases of gonorrhoea have been treated in various parts of the world. Its danger, however, is that in clinical practice if large doses are employed they sometimes cause peripheral neuritis, a condition which sulphanilamide itself does not produce. German clinicians/

clinicians have stated that they avoid this by making use of what they term "stoss" therapy, i.e. the application of short bouts lasting for three or four days and separated by intervals of a week. They do not give more than three "stosses", each one not exceeding fifteen grammes. The daily amount may be given as 3 grammes for 4 days or 4 grammes for 3 days. A special group of cases, 6,000 in all subject to standard tests for cure they say should result in 60-70% being cured after one "stoss", 80-85% after the second, and of the remaining 15-20%, 6-8% (of the total cases) should respond to a third "stoss." Some workers state that they get better results if they start treatment after fourteen days following the first manifestation of the disease when the patient is producing his own immunity against the gonococcus.

Hamilton Wilkie¹ had 100 acute and 20 chronic cases and showed an average clinical success of 75% of cure. D. F. Walsh² had 26 cases with only 1 toxic result - an urticarial rash and sickness - but failed to get a clinical cure in 11 cases.

M & B 693 is now used to a great extent in this country and it is generally agreed that in the treatment of gonorrhoea in the male it is much more therapeutically potent than any of its rivals.

M & B 693 exercises its curative action at a very early/

early stage in the disease. The urethral discharge disappears sometimes in twenty-four hours, and well within a week pus cells no longer appear in the urine. Unlike other sulphanilamides it is not dependent for its maximum effects upon the development of specific immunity, as as a rule in cases adequately treated in their early stages the Complement Fixation test never becomes positive. There are, however, two important points which must be remembered with this successful drug. First, when we give it we stop the discharge in its early stages and we are tempted to reduce the number and variety of our tests and period of observation for cure, and many Authorities remark on the increase in the number of defaulters, as men and women when they secure relief from their acute symptoms and signs do not return to subject themselves to tests for cure and may be still infectious. Other Authorities speak of relapses, especially A. J. Cokkin³ (St. Mary's Hospital), who has seen a genuine relapse as long as eight months after complete early cure, and had also a number of six month relapses as well as three and four month relapses. Secondly, all Authorities agree that M & B 693 must be given in large doses from the very start to have its full effect. General practitioners are apt to begin with .5 gm. t.i.d. and are disappointed with their results./

results. When these patients are sent to the clinic it is found that it is no use starting intensive treatment for at least two weeks after the last dose, as the gonococcus seems to have acquired a resistance to the drug, or the capacity of the liver is such that it can detoxicate a larger proportion of the compound when it is present in the blood in small amounts. Also, these small amounts - as much as .5 gm. t.i.d. - for weeks on end may be definitely toxic without getting the required result.

Since 1938 when May & Baker introduced M & B 693 there have been numerous articles written in this country and in America and all Authorities do not yet agree on the most suitable dose or method of using it. F. J. T. Bowie⁴ treated 31 patients - 30 male and 1 female - of which 23 were suffering from acute urethritis. He gave 3 grammes daily for 4 to 7 days, then 1.5 grammes for another 7 days, combined with urethral irrigation with potassium permanganate, 1/8,000. His results were, 6 cases gonococcus negative in 1 day, 10 in 2 days, 6 in 3 days, 1 in 8 days, and 1 patient did not become negative for 17 days, but there was reason to suppose he was not taking his tablets regularly.

⁵
Batchelor, Lees, and Thompson give a most interesting paper. They found M & B 693 greatly superior/

superior to any other drug they had used, as it produced a more rapid curative effect, toxic effects were less severe, drug resistance was much less common, and the complications were low. In males with acute urethritis they give for 2 days ⁶ 8 grammes a day, 2 days ⁴ 4 grammes, 4 days ³ 3 grammes, and for 6 final days ² 2 grammes. Out of 445 cases 209 (47%) were cured, but 236 (53%) proved to be defaulters, which shows that those who completed treatment had 100% cure. Batchelor, Lees, and Thompson rightly point out that the large numbers who default in the first two weeks present a menace to the success of the sulphanilamides. In all their cases they dispensed with irrigation in any form.

⁶
MacKinnon brings out the point that the object of treatment of gonorrhoea is to attain cure as quickly as possible, and he shows to what extent this has been achieved by M & B 693. In 3,454 men treated by irrigation it took on the average 7.44 weeks to attain cure; with Uleron 5.28 weeks, and with M & B 693, 3.71 weeks. All these cases were treated by irrigation, 1/8,000 potassium permanganate. MacKinnon thinks irrigation important as in his opinion the sulphanilamides seem only to attack the extracellular gonococci and the intracellular are protected, and he attributes the relapsed case which at first is apparently cured to having/

having been re-infected by its own intracellular gonococci lying in urethral crypts which can be got at by irrigation alone.

Albucid, a modification of sulphanilamide produced by the firm of Schering, has also been tried in this country. It is supposed to be less toxic, even in large doses, but as a cure for gonococci it is much weaker. The makers suggest for treatment:-
1st day 15 tablets; 2nd day 12 tablets; 3rd day 9 tablets; 4th day 6 tablets - in all 21 grammes - and they advise delayed chemotherapy.

⁵
Batchelor, Lees, and Thompson tried it with 13 cases and report 4 successes and 9 failures. It would seem, therefore, to be a drug to be used only in those cases where patients cannot tolerate M & B 693 which is too toxic for them.

Proseptasine, the first sulphanilamide to be produced in this country by May & Baker in 1936, has certainly now been superseded by M & B 693.

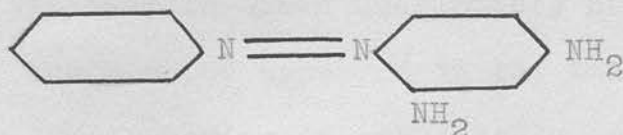
History of the Sulphanilamides

Ever since Ehrlich's discovery of Salvarsan, new remedies for protozoal diseases have appeared at regular intervals. The results have been so encouraging that it was felt it was only a matter of time before a specific drug would be discovered for each disease, but in bacterial infections the outlook has been more gloomy and not much success was expected from chemotherapy. However, in 1935 Professor Domagk⁷ claimed to have discovered a substance with a specific action against streptococci. This substance, a dark red dye, was called Prontosil. The discovery of this substance, however, really goes to the credit of a chemist Gelmo⁸ who, working on the chemistry of dyes in 1908, was the first to mention para amino benzene sulphonamide, but no chemical or clinical trials were made with



this compound. In 1911⁹ Sisley and Porcher showed that chrysordine diamino

azo benzol breaks down in the intestine because of bacterial action, and splits at the double bond.



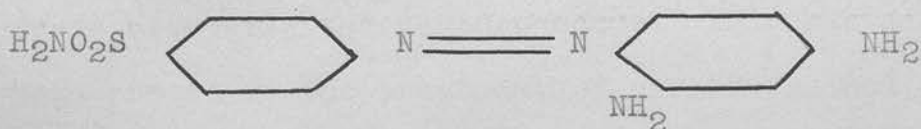
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In 1913 Eisenberg discovered the bacterial power of certain azo dyes, and used them in the treatment of trypanosomiasis.

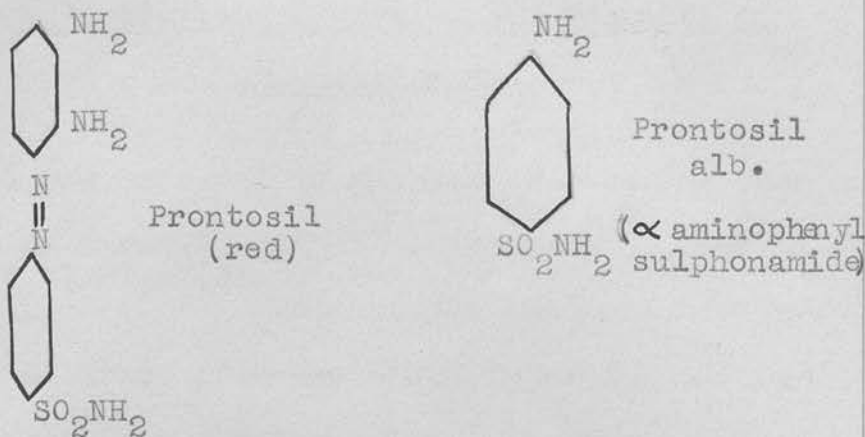
In 1914 scarlet red medicinal toluyl azo toluyl azo beta naphthol was accepted by the Council on Pharmacy and Chemistry of the American Medical Association,¹¹ and was used in the treatment of ulcers to stimulate growth of epithelial cells.

In 1926, Ostromyolensky¹² introduced Pyridium into therapeutics for use in infections of the urinary tract.

In 1932 Meitzsch and Klarer¹³ synthesised an azo dye for the dye industry and obtained a patent. This compound has become known as Prontosil rubrum. It is a sulphonamide 2' : 4' diamino azo benzene, a red crystalline powder.



This led to Domagk discovering its action in streptococcal infection in mice, and so to Domagk rightfully belongs the credit for the discovery of Prontosil as a chemotherapeutic agent in bacterial infection. It was confirmed in this country by workers attached to Queen Charlotte's Hospital,¹⁴ London, and a paper appeared in the Lancet (June 6, 1936) showing its remarkable curative effect in puerperal fever in childbirth.



Later this Prontosil red was simplified to Prontosil album, and an explanation of its action was put forward by Colebrook, Buttle, and O'Meara ¹⁵ who showed that apparently Prontosil itself was reduced to sulphanilamide in the body and acted in the bloodstream. In 1937 H. Proom ¹⁶ found that Prontosil album not only attacked the streptococci, but suggested that it might be of use in cerebro-spinal fever attacking the meningococcus. This has since been proved in the treatment of cerebro-spinal meningitis with M & B 693. In 1936 the firm of May & Baker produced a sulphanilamide called Proseptasine, and in 1939 M & B 693 - Dagenan, as it is now called.

The Absorption, Excretion and Toxicity of
Sulphanilamides.

The pharmacology of sulphanilamides has been studied by Marshall and his co-workers in America. 17,18,19,20,21,22,23.

They proved that sulphanilamide is absorbed from the small intestine and not from the stomach. After taking the drug by mouth the concentration in the blood rises rapidly, reaching a maximum in about three hours and falling to zero in about twenty-four hours. It finds its way into the secretions of the body and all the tissues except bone and fat. It is excreted in the urine partly as the free base and partly in the acetylated inactive form. It is of interest that the rate of elimination is independent of the plasma level but follows the urine flow. It would seem that 70-80% of the drug is re-absorbed into the kidney tubules after filtration through the glomeruli, this making it possible to wash the drug from the system by diuresis in case of overdosage or any toxic symptoms. The marked antigonococcal action of the sulphanilamides does not depend upon the sulphanilamides in the urine. Vest, Hill, Harrill, and Pitts in Baltimore showed in several of their cases of gonococcal urethritis that if the volume of fluid ingested was so restricted that no urine/

urine was excreted during the first twelve hours of treatment, it made no difference as both discharge and gonococci were found to disappear just as rapidly in those cases where urinary secretion was normal.

M & B 693 is absorbed more slowly than sulph-anilamide. It is excreted in the urine, partly as the free base and partly as the acetyl derivative.

Bacteriostatic Action of Sulphanilamide

The latest theory as to the bacteriostatic action of the sulphanilamide is put forward by Woods, Fildes, and Lockwood and Lynch, and commented upon by Bracey and Harper of Liverpool in a letter in the Lancet. In short, their theory is that p-aminobenzoic acid and peptone act as inhibitors of the bacteriostatic action of sulphanilamide. They point out that the bacterial cell, in common with other living organisms, if it is to be kept alive must carry out various metabolic activities which require the presence of certain enzymic systems, varying with the type of bacteria. Now, animal and plant enzymes are susceptible to the action of certain poisons - e.g. cyanides and urethanes - which inhibit their activity. The suggestion is that the same applies to the sulphanilamides and that the enzymic system affected by them is that concerned with the metabolism of nitrogen, which takes place through the intermediary of p-aminobenzoic acid and peptone in the case of streptococcus haemolyticus, and that the rôle of p-aminobenzoic acid and peptone is to form, with the appropriate enzymes, an enzyme substrate complex by virtue of the three chemical factors - NH_2 , COOH , and the benzene nucleus. The enzyme substrate complex is then catalytically broken down with/

with the liberation of the enzyme, which is free to continue with further appropriate substrate, and easily assimilable nitrogen necessary for the life of the organism.

If we examine the chemical structure of sulph-anilamide it is seen that only two of these chemical factors - NH_2 and the benzene nucleus - are present. It has been shown that substances with related chemical structure to that of a normal substrate can combine with the enzyme. The enzyme substrate so formed does not break down, thus preventing the enzyme from combining with the true substrate. This is called in bio-chemistry a "competitive inhibition." In view of this, they state it is reasonable to assume that sulph-anilamide can combine with the same enzyme or enzymes of the bacterial cell to form an enzyme substrate complex which is not broken down and prevents the enzyme so combined from re-uniting with the true substrate (p-aminobenzoic acid and peptone.)

To summarise, when sulph-anilamide is given in human infection its action is as follows:-

- (a) It penetrates to the blood stream in an unaltered form.
- (b) Thus dissolved in the blood and then the other body fluids it goes to the site of infection.
- (c) Bacteriostatic/

- (c) Bacteriostatic action on the organism.
- (d) Direct action on the organism causing degenerative changes mostly in the case of the pneumococci.
- (e) Absorption of the invading organisms by the naturally produced antibodies or leucocytes which are not interfered with by the drug.

Toxicity of the Sulphanilamides.

In the treatment of gonorrhoea with sulphanilamides one must be on the look-out for any toxic symptoms. It might be as well to divide these into their various classes.

General effects. Some patients complain of gastrointestinal symptoms, headache, dizziness, mental depression, and occasionally mental confusion.

Gastro-intestinal symptoms are amongst the commonest symptoms generally mentioned by patients - especially women. Also nausea, actual vomiting, and diarrhoea. Bowie in 1939 reports that with intensive doses the gastric upset may be as high as 66%.

Headache, dizziness, mental depression and confusion. Prebbler in 1938 had 1 case of very severe headache, and Lloyd in 1938 reported headache, dizziness, fainting and depression in 10 out of 108 patients. Various authors advise caution to motorists and airmen who are taking the sulphanilamide as it may completely upset their sense of control and be a danger to themselves and to others.

Skin eruptions. These are rarely severe but may be morbilliform, scarlatiniform, urticarial, and light sensitization. David Erskine ²⁴ gives a paper on dermatitis from sulphonamide compounds in which he suggests that there are two types of cases which may/

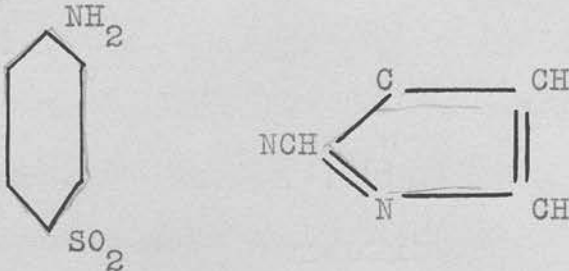
may develop a rash, one which eliminates the drug and may have a true sensitization to it, and the other which retains the drug, and this may be a toxic result by failure of the eliminator. Rupert²⁵ Hallam urges care as the sulphanilamide may in some cases photosensitize the skin and produce a severe rash on exposure to strong sunlight, especially in the tropics, or in ultra violet light treatment.

Haemotopoietic system. The sulphanilamides may affect the bone marrow, and cases may be met with of agranulocytosis and haemolytic anaemia, also sulphaemoglobinaemia or methaemoglobinaemia with cyanosis and slight dyspnoea. Nichol and Freedman²⁶ had a fatal case of agranulocytosis in a male patient who received 68 grammes in 21 days, but generally speaking, reactions of blood condition are mild.

Kidney. Cases have been noted where patients taking the sulphanilamides have had haematuria, but most of these have occurred when the fluid intake was reduced, or in hot climates, as crystals of the acetyl derivative may be formed in the kidneys.²⁷ Cooper and Lewis however, report that owing to the relative insolubility of the sulphanilamides, urinary calculi were found in rats which were given 1 gramme per kg. of body weight. These calculi consisted/

consisted mainly of the acetyl derivative. They point out that although up to the present there has been no evidence of similar effects in man, small deposits may be formed during treatment over a long period until they assume a large size with serious results.

The latest drug of the sulphanilamide group to be introduced is sulphathiazole or M & B 760 produced by May & Baker which has the following formula.



Experimentally and chemically it is less active than M & B 693 in the treatment of pneumococcal infection, and perhaps also in gonococcal and meningococcal infection, but the evidence of nausea, vomiting, and various cerebral effects are seen to be less, so it could be used when M & B 693 is not well tolerated.

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Moeschlin and Hurschler claim it is much less toxic for the red cells than sulphapyridine. They noticed that in the blood of about 50% of patients receiving sulphapyridine some of the red cells when stained supravitaly with brilliant cresyl blue showed a definite intracorpuscular granule situated as/

as a rule at the periphery of the cells. In patients treated with sulphathiazole the red cells did not show these granules. The nature of these intracorpuseular granules is not known but they have been found when methaemoglobin formation has occurred and may be produced by haemolytic drugs: they seem to be definitely connected with the toxic action on the red cells and hence the authors conclude that sulphathiazole is less toxic than sulphapyridine. They give a chemical explanation and suggest that the absence of the pyridine ring makes it less toxic to red cells. Sulphathiazole is excreted more rapidly than sulphapyridine and the maximum concentration of sulphathiazole in the serum is neither so high nor maintained for so long, so Gaisford and Whitelaw²⁹ suggest in pneumonia giving sulphapyridine at first to get maximum concentration and gradually to replace with sulphathiazole in subsequent doses, which course might be adopted in gonorrhoeal infections.

³⁰
V. C. Lloyd and David Erskine have tried it in gonorrhoea with good results. Response to treatment was rapid and there was no evidence of intolerance. They gave 4 grammes daily for 5 days to 19 patients. In 13 cases the discharge cleared up in 2 days, and in only 1 case was it prolonged beyond 5 days. Of the 19 patients, 14 were under observation/

observation for 5 to 9 weeks, and there was no recurrence. The other 5 were defaulters, but there is no reason to suppose they were not cured.

J. Gaté and Pluillaret³¹ reported good results in the treatment of acute gonorrhoea with sulphathiazole. Up to December 1939 they had treated 68 patients, 9 grammes were given over 24 hours, and a single day's treatment rapidly cleared the gonococci from the urethra with^{out} any local measures. All the patients were cured as established by a careful follow-up with provocative tests. Tolerance was good. There was one case of cyanosis.

There appears to be no specificity in the action of any of these drugs in bacterial infection. One drug is not better for one type of infection and another for another type, as is the case in protozoal disease where we find quinine active against malaria, and the arsenicals in spirochaete infection.

Treatment of Gonorrhoeal Infections - The Male.

Before treatment is started the patient's personal history is enquired into, his age, occupation, whether he is married or single, and if he has had previous attacks of venereal disease. An endeavour is then made to find out the approximate date of infection and the date of appearance of the first symptoms. A full clinical examination is carried out. Smears are made from the urethral discharge, if any, by Gram's method (Jensen's modification) and examined at once. The urine is then passed into two test glasses and it is noted if these are cloudy or clear so as to eliminate posterior infection. If doubt exists regarding the diagnosis, blood is taken for the gonococcal Complement Fixation test and cultures of the secretion made. If the smear is positive, M & B 693 is given at once. Delayed chemotherapy is not practised. Irrigation with potassium permanganate, 1/8,000 is also started immediately at the clinic. If possible, the patient attends every evening for a week to irrigate under supervision of the orderly, or is instructed personally how to use a home irrigator which is provided at cost price. The dosage is as in the table.

Dosage in Grammes.

<u>Days</u>	<u>Males</u>	<u>Females</u>
1	3	3
2	3	3
3	3	3
4	3	3
5	3	3
6		3
7		3
	Total 15 Gms.	21 Gms.

In females who do not always tolerate the drug as well as males, the dose would read 2 grammes instead of 3 grammes, and the total would be 14 grammes.

There are several points about dosage which must be impressed upon the patients.

- (1) They must take the tablets at certain fixed times so that the drug will be in the blood stream at its maximum all the time, say at 7 a.m., 12 midday, and 6 p.m. - 2 tablets of sulphapyridine (M & B 693). Night workers would take them at different times.
- (2) They must go on taking them even if they feel sick or have other symptoms, or else report at the clinic for further advice before the supply is finished.
- (3) They must take only 2 at a time as ordered, not 3 or 4 at once if they forget a dose.
- (4) If they feel sick after a dose they should take the subsequent dose with a large draught of still lemonade sweetened with glucose.

I find with sulphapyridine that the prohibition of food or drugs rich in sulphur is unnecessary, but no alcohol must be taken until allowed.

The patient reports in a week's time and enquiries are made as to any toxic symptoms. He is then examined for any discharge, and if present this is examined. Urine is passed into two glasses, and it is noted whether this is clear or cloudy. If there is no discharge and both glasses are clear, all treatment is stopped. The following week the same tests are done and if negative the patient is given a provocative dose of 200 million gonococcus vaccine - St. Thomas' Hospital brand marketed by Boots - and told he may take alcohol. He is fully examined again the next week, and if negative the prostate and seminal vesicles are massaged and any discharge examined for gonococci. If clear, he reports the following week and bougies are passed, 16/20 French gauge posterior, and the largest the meatus will admit anterior, and the urethra is massaged over them. If after examination a week later there are no symptoms of recurrence he is discharged as cured.

If I find after a week's intensive course of sulphapyridine that there is still a discharge which is positive, I give another course and have rarely found this does not cure a patient. Some patients/

patients are, however, "drug resistant", i.e. partially or completely unaffected by the drug. These patients may be divided into three main groups.

A Those who have had previous inadequate treatment with sulphapyridine or other sulphanilamides (1 tablet 3 times a day). It is better to wait at least fourteen days before beginning again with adequate doses and to rely in the meantime on irrigation with potassium permanganate 1/8,000 and vaccine treatment.

B Those who because of mild toxic symptoms do not persevere with the drug and take inadequate doses. Here one must impress upon the patients the importance of taking the drug as ordered. They must start the treatment again after fourteen days, relying until then on irrigation and vaccines.

C Those who have any complications such as gonococci buried in the crypts in the urethra. These may well be the intracellular type of gonococci mentioned by D. J. MacKinnon, which in his series of cases seemed resistant to the sulphanilamide, and this will clear up after massage of the urethra over bougies, and massage of the prostate and seminal vesicles per rectum. If during treatment there is a relapse in any of the/

the patients, with a positive smear, and fourteen days have elapsed since the patient has taken sulphapyridine, he restarts treatment and goes through the five weeks' course. If serious toxic symptoms appear during the treatment it is understood that the blood will have to be examined in cases of cyanosis or breathlessness, the urine for blood if there were nephritic symptoms, and the skin if rashes appeared. All these complications would indicate overdosage or non-elimination, or an idiosyncrasy to the drug, and the treatment would have to be suspended for the time being, the patient continuing with simple irrigation and an alkaline mixture and vaccines.

The Gonococcal Complement Fixation Test.

I have employed this test in several cases but find that with the sulphanilamides its use is limited, as when it is understood that the test is a serum reaction which registers the presence or absence of specific gonococcal antibodies in the blood, and that these are rarely present in the early uncomplicated stages of the disease if adequately treated with sulphapyridine, one finds the test is nearly always negative. But for determining cure, a series of these tests is most useful, as a strongly positive, diminishing gradually to negative, is very good evidence of cure. Also, at a certain stage in the disease (varying in different people) a positive Gonococcal Complement Fixation test is regarded as being a good sign, showing the presence of antibodies, and that natural immunisation is taking place. Similarly, a negative result may be a bad sign if the disease has been present for a number of weeks or months. And in the neglected case when the disease has reached the posterior urethra with involvement of the seminal vesicles and prostate which may lead to a condition of "closed" infection, and the material is absorbed into the blood stream, we get a strongly positive Gonococcal Complement Fixation test, and without positive clinical signs such as a discharge, the test is of great importance.

Treatment in Women.

Here the chemotherapy is the same but women require different management and estimation of cure. I find they report toxic symptoms more than men, especially headache and nausea, but I endeavour to give the same dose and for seven days instead of five as they seem more resistant to the drug. The personal and clinical histories are taken, and whether married or single - an important point for later re-infection by the husband. Then smears are taken from the urethra and cervix uteri, and if required, from Bartholin's gland. These are sent to the adjoining Pathological Department, but if from the history and clinical signs gonorrhoea is suspected, treatment is begun at once. Blood is taken for the Gonococcal Complement Fixation test, and vaginal douching and urethral irrigation are carried out with a glass nozzle of the London Hospital pattern. Potassium permanganate 1/8,000 is used for both as a routine. This is done daily at the clinic or at home. Usually only vaginal douching is demonstrated, but in exceptional cases urethral douching is also demonstrated. If the smear taken at the start is positive, the patient reports every week for seven consecutive weeks. Smears are taken at these intervals and the Gonococcal Complement Fixation test at the sixth week. If/

If the patient has a negative smear, however, but a positive Gonococcal Complement Fixation test after clinical signs have disappeared, the Gonococcal Complement Fixation test is repeated monthly until negative.

Cases and Discussion.

In the study of cases of gonorrhoea treated with sulphanilamide, I have attempted the following procedure. In assessing its value I was of the opinion that the best method would be to compare in detail the treatment of patients in the pre-sulphanilamide days (i.e. with irrigation and an alkaline mixture), the sulphanilamide days, with sulphapyridine (Dagenan M & B 693), and with the latest drug sulphathiazole or "Thiazamide" (M & B 760). On looking up old cases I find the first series to be treated consistently with sulphanilamide was begun on December 29th 1937, and the last on the 25th August 1938, eight months in all during which 60 cases were treated, the majority being male. I then chose the 60 before those, treated by irrigation and vaccines and the 60 following, treated by sulphapyridine (M & B 693), and lastly the few treated by sulphathiazole (M & B 760). These four groups, three of 60, I tabulated under thirteen headings (see over), which I hoped would give me sufficient data to work on. To see how the cases treated this year by sulphapyridine (M & B 693) had fared, I also took all the cases discharged and who ceased to attend after completion of treatment up to September 30th 1940, when I was writing this thesis. At this point, before/

before discussing the results I obtained, I think it necessary to define some terms I have used.

Cured or Discharged - Discharged after completion of treatment and observation (including routine tests).

Ceased A or Defaulters - Any patient who ceased to attend before completion of treatment.

Ceased B or Apparent Cures - Any patient who ceased to attend after completion of treatment but before completion of observation period and tests.

Relapse - Any patient who has a return of symptoms and signs, with a positive smear, who as far as could be established had not re-infected himself.

Drug Resistant - Where the patient with adequate doses of the drug still continues with a positive smear. This is, in most cases, acquired when the patient has been previously treated with inadequate doses of the sulph-anilamides, or had a closed infection after complications.

It might be as well here to give the treatment adopted in this series of cases.

A. Pre-sulphanilamide Treatment. Daily irrigation with 1/8,000 potassium permanganate for 3 weeks or/

or as long as the discharge continues, and an alkaline mixture and vaccine treatment.

B. Sulphanilamide Treatment.

1st week 1 gm 3 times a day)
 2nd " 1 gm " " " ") 52½ gms.
 3rd " .5 gm " " " ")

All with irrigation with 1/8,000 potassium permanganate.

C. Sulphapyridine Treatment (M & B 693).

See previous "Treatment of Gonorrhoeal Infection."

Now let us discuss the 180 cases in more detail and tabulate them.

	<u>Results of Treatment</u>			<u>Males</u>
	<u>No</u>	<u>Cures</u>	<u>Apparent Cures</u>	<u>Defaulters</u>
Irrigation & Mixture	60	33(55%)	11(18%)	16(26%)
Sulphanilamide & Irrigation	60	26(43%)	16(26%)	18(30%)
Sulphapyridine (M & B 693)	60	30 (50%)	12(20%)	18(30%)

	<u>Males</u>				
	<u>No</u>	<u>Drug Resist.</u>	<u>Compli-cation</u>	<u>Re-lapses</u>	<u>Toxicity</u>
Irrigation & Mixture	60	-	?	12(20%)	-
Sulphanilamide & Irrigation	60	2(3%)	9(15%)	12(20%)	16(26%)
Sulphapyridine (M & B 693)	60	5(8%)	7(11%)	6(10%)	28(46%)

Table 3

Males Cured

	<u>No.</u>	<u>average</u>	<u>Days under Treatment</u>
Irrigation & Mixture	60	"	75
Sulphanilamide	60	"	55
Sulphapyridine (M & B 693)	60	"	52
Up to Sept 30, 1940.	15	"	41

Table 4

Males

	<u>No</u>	<u>Length of time for discharge to clear up</u>
Irrigation & Mixture	60	28 days
Sulphanilamide	60	7-12 "
Sulphapyridine (M & B 693)	60	1-2 "

In 23 cases (38%) dry the day following.

Table 5

Males

Cases Cured and Apparently Cured (Ceased B) up to Sept. 30, 1940

	<u>No</u>	<u>Cured</u>	<u>Appar. Cured</u>	<u>Days under treatment for Cured Cases</u>	<u>Dry in 48 hrs</u>	<u>Toxi-city</u>	<u>Re-lapse</u>
Sulphanilamide (M&B 693)	25	15	10	41 days	16	9	1

2 cases - one with a positive Gonococcal Complement Fixation test and the other with epididymitis - took 293 days to be discharged. These are not included in the above.

Now/

Now let us analyse these tables a little more fully from the point of view of percentage. To my surprise, we seem in Table 1 to have had more cures with irrigation and medicine than with the sulph-anilamides but I think this may well be explained by looking at Tables 3 and 4. In Table 3 we see that with irrigation the average time for cure is seventy-five days, while with the sulph-anilamides the average time for cure is roughly fifty days. We therefore keep an eye on the patients for a longer period, and they get into the habit of coming to the clinic for irrigation daily. What I think is of more importance is that the discharge with the sulph-anilamide is cleared up in a day or two, or in the case of sulphapyridine (M & B 693) in adequate doses in 38% of cases in twenty-four hours as shown in Table 4 and 5. The patient, feeling well and with no discomfort or discharge, discharges himself however much he is advised to report again. In Table 1 this point is brought out when we get with the sulph-anilamides 30% of defaulters, and it is to be hoped that these 30%, and the 26% and 20% of apparent cure are definitely cured and have not spread gonorrhoea to the community. In comparing sulph-anilamide with sulphapyridine (M & B 693) regarding cure we find sulphapyridine cures 50% of cases and sulph-anilamide 43%. If we add/

add apparent cures to the former we get 70% and to the latter 69%. There is therefore not much to choose between them except that with sulphapyridine you get your result with, in most cases, 15 grammes of sulphapyridine, and $52\frac{1}{2}$ grammes of sulphanilamide - the latter with more risk of toxic effects, or of the patient neglecting his treatment.

Relapses, Complications, and Drug Resistance.

I have grouped these three together because in several of the cases of relapse it has been found that this was due to inadequate doses of sulphanilamide previous to attending the clinic. I have included in the relapses those cases which relapsed after sulphanilamide or after sulphapyridine before reaching the clinic. In most other cases the relapses were due to some complication either arising during the treatment, which was rare, or already existing when the patient came under observation. These relapses are so important that I will give them in some detail.

Case 1

A man aged 34 came to the clinic on the 23rd August 1937. There was a copious urethral discharge of pus which had started the same day. This was found to be G.C.†. Posterior irrigation with 1/8,000 potassium permanganate was begun and an alkaline mixture given. This treatment was continued/

continued until the 13th September when all discharge had ceased. Tests for cure were undertaken, but on the 1st December the discharge recurred (G.C.+). Irrigation was resumed and 1 gramme of sulphanilamide was given 3 times a day for 1 week. The next week he had no discharge and another 1 gramme 3 times a day was given. He subsequently discharged himself but on the 16th January 1938 he was re-admitted with a copious urethral discharge (G.C.+). He was again given sulphanilamide in the usual dose for 3 weeks - $52\frac{1}{2}$ grammes - but in the course of observations for cure had a slight discharge on the 14th March which was G.C.+ . Irrigation was resumed and a vaccine given up to 400 millions on the 13th April, when he discharged himself again, one hopes cured.

Comment A case given adequate treatment with sulphanilamide and having no complication which relapsed three times.

Case 2

A Labourer aged 26 came to the clinic on the 6th February 1938 with a copious urethral discharge (G.C.+) which had started on the 6th February. He had had no previous treatment. He was put on the usual dosage of sulphanilamide, suffered no toxic effects, and was dry on the 9th March. On the 14th March the discharge re-commenced (G.C.+).
Irrigation/

Irrigation was started again and a vaccine given. He came to the clinic on the 13th April with a discharge which had started again on the 11th April. This was also G.C.+ . Vaccine treatment was continued, but on the 11th May he had difficulty with micturition, but no discharge. On the 18th May his trouble with micturition became worse, and on examination his seminal vesicles were painful. He was given Uleron for 4 days - 1 gramme 3 times a day. On June 8th all symptoms had cleared up and he was discharged on the 13th July.

Comment A case given adequate treatment with sulphanilamide which relapsed evidently with the complication of vesiculitis but cleared up with Uleron and vaccine treatment.

Case 3

A Farmer aged 31 came to the clinic on the 16th February 1938 with a copious urethral discharge (G.C.+) which had started on the 25th December 1937. He had had no previous treatment. He was given the usual sulphanilamide treatment and irrigation, and the discharge cleared up on the 2nd March. He came to the clinic on the 16th March with a discharge (G.C.+) which had started again on the 12th March after influenza. He was given vaccine treatment and irrigation, but having been dry on the 23rd March had a copious discharge (G.C.+)
on/

on the 30th. Irrigation was resumed and vaccine treatment continued. He was dry on the 21st April but came to the clinic on the 1st June with a copious discharge (G.C.+) which had started on the 28th May. He was examined per rectum and his seminal vesicles were very painful. Irrigation was again carried out and on the 23rd June his symptoms were gone. On the 6th July he had a copious discharge (G.C.+) with painful prostate and seminal vesicles. He was given Uleron, 1 gramme 3 times a day for 1 week. The discharge ceased but on the 3rd August he had a slight urethral discharge (G.C.+) and was given M & B 693, 1 gramme 3 times a day for 10 days. He had a violent headache so only took them for 6 days. These cleared up the discharge, and having passed all tests he was discharged on the 14th September 1938.

Comment A case given adequate treatment with sulph-anilamide which relapsed after influenza; again relapsed after vesiculitis, failed to be cured with Uleron but was cured with adequate doses of sulphapyridine (M & B 693).

Case 4

A Labourer came to the clinic on the 23rd February 1938 with a copious urethral discharge (G.C.+) which started on the 10th February. No previous treatment. He was apparently cured with

42 grammes sulphanilamide on 16th March 1938, discharged himself, but came to the clinic on the 22nd June with a urethral discharge (G.C.+). He was also suffering from arthritis of the knees. He was apparently cured with $52\frac{1}{2}$ grammes sulphanilamide on the 20th July, but discharged himself while under observation.

Comment. A case given adequate treatment with sulphanilamide which relapsed. There was a possibility of re-infection from his wife, an old patient, but the arthritis may have caused his relapse.

Case 5

A Gardener aged 18 came to the clinic on the 10th March 1938 with a copious urethral discharge (G.C.+), which had started on the 9th March. No previous treatment. He was treated with $52\frac{1}{2}$ grammes sulphanilamide but relapsed with a urethral discharge (G.C.+), on the 6th April, 25th May and 15th June, when he had balanitis. He was given 3 "stosses" of Uleron for 4 days, and after the last failed to report. One hopes he was cured.

Comment. A relapse after adequate doses of sulphanilamide, and perhaps cured with Uleron after balanitis.

Case 6

A Baker aged 29 reported at the clinic on the 21st March 1938 with a copious urethral discharge (G.C.+)/

(G.C.†) of one day's duration. He was treated with $52\frac{1}{2}$ grammes sulphanilamide but relapsed on the 4th May 1938 with slight urethral discharge (G.C.†). Bougies had been passed the week before. He discharged himself on the 11th May 1938 with a slight negative discharge.

Comment A relapse after adequate doses of sulphanilamide and after passage of bougies. Possible infection of Littré's glands. Discharged himself, most likely in an infectious condition.

Case 7

A Labourer aged 40 reported at the clinic on the 9th March 1938 with a copious urethral discharge (G.C.†) of five days' duration. Treated with $52\frac{1}{2}$ grammes sulphanilamide and bougies passed on the 6th April. Resolved Littré's glands, palpable, not tender on passage. No discharge afterwards, but on the 13th May slight urethral discharge (G.C.†). He was discharged on the 1st June 1938. On the 13th July he again came to the clinic with a history of discharge dating from the 9th July. On examination there was a urethral discharge (G.C.†). He was given sulphapyridine (M & B 693), 1 gramme 3 times a day, and discharged himself on the 17th August 1938 after bougies had been passed.

Comment A relapse with sulphanilamide after infection of Littré's glands. Apparently cured by sulphapyridine (M & B 693).

Case 8

A Steel Erector aged 36 came to the clinic on the 30th March 1938 with a copious urethral discharge (G.C.†) of one day's duration. Treated with $52\frac{1}{2}$ grammes sulphanilamide. Bougies passed on the 27th April. Relapsed (G.C.†) on the 4th May. Discharged himself on the 12th June 1938.

Comment A case very similar to No. 7.

Case 9

A Chauffeur aged 32 reported at the clinic on the 2nd June 1938 with a copious urethral discharge (G.C.†) of seven days' duration. No previous treatment. Treated with sulphanilamide, $52\frac{1}{2}$ grammes. Slight discharge with pus cells until the 22nd June. Copious urethral discharge on the 29th June (G.C.†). Given vaccine treatment, and discharged himself on the 3rd August apparently cured.

Comment A relapse after sulphanilamide, no complications but discharge with pus cells continued for some time, becoming positive.

The following three cases relapsed after sulphanilamide but were discharged cured with sulphapyridine (M & B 693).

Case 10

Male attended the clinic on the 15th June 1938 with copious discharge (G.C.†). Relapsed on the 28th July after sulphanilamide, $52\frac{1}{2}$ grammes. Given sulphapyridine/

sulphapyridine, 21 grammes a week and 12 grammes for 4 days. Discharged on the 8th September cured.

Case 11

Male came to clinic on the 7th July 1938 with a copious discharge (G.C.+). Relapsed on the 3rd August after sulphanilamide, $52\frac{1}{2}$ grammes. Given sulphapyridine, 21 grammes a week and 12 grammes for 4 days. Discharged on the 14th August cured.

Case 12

Male attended the clinic on the 16th June 1938 with copious urethral discharge (G.C.+). Given $52\frac{1}{2}$ grammes sulphanilamide. Relapsed on the 13th August. Given sulphapyridine, 21 grammes a week and 12 grammes for 4 days. Discharged on the 7th September cured.

Case 13

This case is of some interest so is given in more detail. A Joiner aged 50 came to the clinic first on the 25th August 1937 with a copious urethral discharge (G.C.+) of one week's duration. He had been given medicine by his private practitioner which had failed. He also had paraphimosis and was put on twice daily irrigation with potassium permanganate. The copious discharge continued, and on the 15th September he complained of pain in both testicles. On the 22nd September he had a right epididymitis which was treated with ichthyol and glycerin /

glycerin and 1 c.c. Antitoxin (Park Davis & Co.) which cleared up the epididymitis. On the 29th September he had a slight purulent discharge (G.C.+) which disappeared on the 13th October and he was discharged on the 24th November 1937. He was re-admitted on the 14th July 1938 stating that the discharge had recurred on the 11th and that he had pain on micturition. On examination, he had a clear discharge, very slight G.C.--. His G.C.F. however was strongly positive. On the 27th July he was given sulphaniilamide, 1 gramme t.i.d. for a week, but was unable to take it owing to old gastric trouble. He was told to report for G.C.F. in two months' time. He returned on the 29th September and his G.C.F. was again positive. He reported on the 13th October and was put on 2 "stosses" of Uleron, 1 gramme 3 times a day for 4 days. On the 10th November he was feeling very well, no discharge, but G.C.F. still positive. On the 27th July he reported for a G.C.F. and this was negative.

Comment This cure is of interest for two reasons. Firstly, that a man who could not tolerate sulphaniilamide because of old gastric trouble was not upset by Uleron. Secondly, it shows the value of the Gonococcal Complement Fixation test for cure in long-standing cases, and if one has the co-operation of the patient, he can be given a certain cure even after 2 years.

Drug Resistant Cases and Relapses.

The following cases are some which relapsed or which have not been cured by inadequate doses of the sulphanilamides, i.e. drug resistant cases.

Case 1

A Van Driver aged 29 was sent by his doctor on the 12th December 1938 because treatment had failed. It was found that he had had an initial treatment of 1 tablet sulphanilamide 3 times a day from the 8th December. There was a copious urethral discharge (G.C.+). Posterior irrigation with potassium permanganate 1/8,000 was begun, and 1 gramme sulphapyridine (M & B 693) was given 3 times a day for 5 days. All clinical signs disappeared on the 21st December. The G.C.F. was done and was negative. He was discharged cured after all tests on February 1st 1939. On the 2nd March 1939 he was re-admitted stating that on two occasions he had had a slight urethral discharge. On examination, there was a definite slight discharge (G.C.+). The G.C.F. was still negative. He was given 1 gramme sulphapyridine (M & B 693) 3 times a day for 1 week. Clinical signs ceased on the 9th March and he was discharged cured on the 5th April 1939 having passed all tests for cure.

Comment A typical case of drug resistance resulting from inadequate doses.

Case 2

A Joiner aged 27 was sent by his medical attendant on the 11th January 1939 because treatment had failed. It was found that he had had an initial course of streptocide, 4 tablets daily, since the 28th December 1938, but the discharge had never ceased. He had had no tablets for 4 days before coming to the clinic. On examination he had a purulent urethral discharge (G.C.+). Posterior irrigation with potassium permanganate 1/8,000 was begun, and he was given sulphapyridine (M & B 693), 3 grammes for 5 days. He reported on the 10th January stating that he had for some reason only taken 4 tablets and still had a copious discharge of pus (G.C.+). The dose of sulphapyridine (M & B 693), 3 grammes daily was repeated, and he went through all the tests until the 15th February 1939. On the 27th February he again had a purulent discharge (G.C.+) and was given sulphapyridine (M & B 693), 3 grammes daily for 7 days. All clinical signs disappeared in 1 week, and having gone through all the tests for cure he was discharged on the 5th April 1939.

Comment Another typical case of drug resistance owing to inadequate doses, showing also that it is no use giving adequate doses after too short an interval before the patient loses his drug resistance/

resistance. Irrigation must be relied upon in the interval, and vaccine treatment.

Eight other cases came to the clinic, 6 in 1939 and 2 in 1940, having previously been given inadequate doses, and these are tabulated below.

<u>Sex</u>	<u>Age</u>	<u>Previous Treatment</u>	<u>1st Attendance</u>	<u>Relapse</u>	<u>Result.</u>
1. Male	24	$\frac{1}{2}$ gm. sulphanilamide t.i.d.	30.1.39 G.C.+	Nil	Discharged 8.3.39.
2. Male	31	4 tablets daily M & B 693 21.1.39. to 23.1.39. 2 tablets daily M & B 693 26.1.39 to 2.2.39.	9.2.39 G.C.+	Nil	Ceased B 8.3.39.
3. Male	20	M & B 693 4 tablets daily for 9 days.	31.3.39 G.C.+	20.11.39.	Transferred 12.4.39.
4. Male	37	Sulphanilamide 1 t.i.d. for 4 days.	9.11.39 G.C.+	4.12.39.	Ceased B 10.1.40.
5. Male	19	Sulphanilamide 6 tablets daily for 7 days 31.10.39. 4 tablets daily for 7 days 6.11.39. M & B 693 4 tablets daily for 4 days.	22.11.39. G.C.+	13.12.39.	Ceased B 20.12.39.
6. Male	27	Dean St. Hospital M & B 693? discharged 6 mths ago.	20.12.39. G.C.+	3.1.40.	Ceased A 24.1.40.

<u>Sex</u>	<u>Age</u>	<u>Previous Treatment</u>	<u>1st Attendance</u>	<u>Relapse</u>	<u>Result</u>
7. Male	38	M&B 693, 2 t.i.d. for 4 days M&B 693, 1 t.i.d. for 8 days. Interval 2 days. M&B 693 1 t.i.d. for 7 days	21.2.40 G.C.+	13.3.40 3.4.40 G.C.+	Ceased B 5.6.40
8. Male	33	M&B 693 4 tablets daily for 4 days	10.7.40 G.C.+	Nil	Ceased A 10.7.40

In these eight cases 2 who discharged themselves - cases 6 and 8 - were most certainly still infective.

On looking up sixty previous cases at the clinic I could find only one which relapsed without complication after adequate doses of sulphapyridine (M & B 693).

A Gardener aged 40 came to the clinic on the 26th April 1939 with a copious purulent discharge (G.C.+) which had started on the 12th April. He had had no previous treatment. He was given sulphapyridine, 3 grammes daily for 5 days, and irrigation. All clinical signs disappeared in a week, but the following week he again had a discharge (G.C.+) and was given sulphapyridine, 3 grammes daily for 7 days. The week after, clinical signs again disappeared, but unfortunately he then discharged himself without undergoing tests for cure.

Comment A case treated adequately with sulphapyridine (M & B 693) which relapsed for no explained reason.



Cases with Toxic Symptoms

In the cases which I have reviewed treated with sulphanilamide and sulphapyridine (M & B 693), toxicity has never been marked but has been more in evidence with sulphapyridine (46%) than with sulphanilamide (26%). Headache was the chief complaint in 7 patients treated with sulphanilamide and in 11 patients treated with sulphapyridine. Rashes followed the sulphanilamide treatment in 6 cases, and in 1 case after sulphapyridine. This is what one might expect on comparing the different doses, 52½ grammes and 15 grammes. I had no case of nausea or sickness with sulphanilamide, but 3 cases of nausea and 6 with actual vomiting after sulphapyridine (M & B 693). 1 case of dizziness occurred with sulphanilamide, and 5 with sulphapyridine. The last complaint, tingling of the hands and feet, was uncommon in both sulphanilamide and sulphapyridine.

Comparing these results with those of other workers, I found in the case of F. J.⁴ Bowie that out of 30 cases treated with the same dose of sulphapyridine (M & B 693) he had 7 toxic results. He had only 1 case of headache to my 11 cases in 60; 2 cases of nausea to my 3, and he had no case of actual vomiting whereas I had 6. Scottish stomachs must be stronger than English! He had 2 cases of dizziness to my 5, and no case of rash as compared with/

with my 1 case. He reports, however, 1 instance of breathlessness in a patient and 1 instance of drowsiness, complaints I did not encounter. Somerville³² after using the same dose of sulphapyridine had 76 cases out of a total of 152 which showed toxic symptoms, which are much the same results as mine, as also are his headache results of 26. To his 3 instances of vomiting and 30 of nausea I had 6 cases of vomiting and 3 of nausea. His rashes were 3 to my 1 in half the cases, and his instances of dizziness were 6 to my 5. Somerville states that he thought his dose, 3 grammes daily, produced too toxic effects. He reduced it to 2 grammes, and claims as good results.

The Gonococcal Complement Fixation Test.

This test is most useful as an aid to diagnosis in the absence of a positive microscopic test, as the following case shows.

A Motor Driver aged 30 reported at the clinic on the 5th April 1939 with the following history. In January 1935 he had been treated at the Aberdeen clinic for eight weeks by irrigation with potassium permanganate but was not discharged. His smear was said to be negative, and he had had no urethral discharge since. On examination there was no discharge but his G.C.F. was strongly positive and he was given 3 grammes sulphapyridine (M & B 693) for 1 week. On the 31st May his G.C.F. was still strongly positive but on the 30th August came down to weakly positive, and finally on the 25th October to negative.

Comment A case with no clinical signs but found to have a strongly positive G.C.F. which was brought to negative in seven months by a full dose of M & B 693. A G.C.F. should therefore always be done in suspicious cases with a G.C.--. smear.

The G.C.F. as a test for cure is not, however, a routine with the sulphanilamides, as when these are given early, in adequate doses, a positive result is never obtained. When the disease has been present for a month or more before treatment is begun/

begun, the test is worth doing as there is some prospect of it having become positive. If a positive result is obtained the test is repeated at intervals of one or two months until negative, but in the absence of all clinical signs it is, I think, permissible to discharge a patient without waiting for a negative report if a descending series is obtained.

I have one patient in mind, however, who has had no discharge, and clinically has been cured for years. The patient had an infection of the seminal vesicles which cleared up, but since 1937 he has had a strongly positive G.C.F. despite all treatment. I do not feel justified in advising surgical treatment for removal of one of the vesicles, though this might cure him as regards his strongly positive G.C.F.

In my series, this test was used on twelve occasions with sulphanilamide treatment, and in most cases it brought a strongly positive reaction down to a negative, or at least a doubtful negative when the patient could be persuaded to report at monthly or two monthly intervals (see case 13).

In the sulphapyridine series the test was used in nine cases, but here most of them were negative to start with.

Thiazamide (Sulphathiazole) M & B 760.

I have only had the opportunity of using this drug in fourteen cases, as there is difficulty in getting it owing to war conditions. So far as it is possible to judge from this limited experience, sulphathiazole promises to be the drug of choice in gonorrhoea. Much greater experience will be required, however, before any definite conclusion can be reached. One of the advantages is that very large doses can be given in a short period of time, and a cure might be effected in twenty-four hours.

In these fourteen cases of twelve males and two females receiving the same dose - 8 tablets daily for 2 days and 6 tablets daily for 3 days, 34 tablets in all ($17\frac{1}{2}$ gms.) - the only toxic symptom occurred in a male who complained of listlessness. In 9 male cases the discharge ceased in 24 hours and in 3 cases in 48 hours. In one case, an intelligent male, I tried the intensive treatment as advocated by J. Gaté³¹ and Pluillaret - see case 2 - but he had a relapse. The two female cases responded well to treatment.

I now detail those cases of special interest.

Case 1

A Gardener-Chauffeur aged 24 came to the clinic on the 25th September 1940. There was a copious urethral discharge (G.C.+). Sulphathiazole was given/

given as follows:- 2 tablets 4 times a day for 2 days, and 2 tablets 3 times a day for 3 days - 34 tablets in all. No local treatment was carried out. All clinical signs disappeared on the 2nd October. The patient stated that the discharge ceased on the 26th September and that he had no toxic symptoms. He drank, contrary to instructions, considerable quantities of beer on the 27th September. He was given a provocative vaccine of 200 million on the 9th October and discharged himself, one presumes cured.

Case 2

A Bricklayer aged 25 came to the clinic on the 11th December 1940 with a purulent urethral discharge G.C.†. He was given sulphathiazole (M & B 760), 3 tablets every 4 hours day and night for 24 hours - 9 grammes in all - and daily irrigation with potassium permanganate 1/8,000. When he reported on the 12th December there was no discharge; the first glass contained threads and the second was clear; there were no toxic symptoms. On the 18th December he had a purulent discharge G.C.† and he was put on the usual dose of 8 tablets daily for 2 days and 6 tablets for 3 days. He came to the clinic on the 1st January 1941, quite dry, and stated that the discharge had ceased on the 19th December. All treatment was stopped and he continued/

continued to be free from discharge. He reported on the 8th January 1941 and was given a provocative dose of 200 million Vacc.A. He is still undergoing tests for cure.

Comment A patient given intensive treatment with sulphathiazole who relapsed but so far has been cured with the ordinary dosage as adopted at the clinic.

Case 3

A married woman aged 27 who had been infected by her husband (under our care) came to the clinic on the 14th October 1940. On examination there was no urethral discharge but slight leucorrhoea. The urethral smear was G.C.--. but the cervical smear was G.C.+ . She was given sulphathiazole, 8 tablets daily for 2 days and 6 tablets daily for 5 days and home irrigation with potassium permanganate 1/8,000, and her blood taken for the G.C.F. test. On reporting on the 21st October there was no urethral discharge but a slight leucorrhoea. She had had no toxic symptoms whatever. Smears taken were G.C.--. and the G.C.F. doubtful. On examination on the 4th November there were no signs and her smears were again negative. Her blood was re-taken and the G.C.F. was negative. On the 9th December she was again examined and smears taken which were G.C.--. She then left the district, we hope cured.

Comment/

Comment A female with a doubtful G.C.F. and a positive cervical smear given sulphathiazole for a week, without toxic symptoms, and presumed cured.

Case 4

A Barmaid aged 21 came to the clinic on the 12th December 1940. On examination smears were taken from the urethra and cervix. The former was G.C.+ . She was given sulphathiazole, 8 tablets daily for 2 days and 6 tablets daily for 3 days, and daily douching with potassium permanganate 1/8,000. The G.C.F. was negative. On the 23rd December the smears were negative and she had no toxic symptoms. On the 28th December the smears were again negative, and though she is still under observation, one hopes she is cured.

Comment A female with a positive urethral smear given sulphathiazole without toxic symptoms. Still under observation but presumed cured.

The Sulphanilamides in Gonorrhoea in Women.

I shall discuss women separately because although the chemotherapy is the same, the onset, course, and tests for cure differ to a great extent. On learning the history, rarely is a case found to be acute. They so often prove to be sub-acute from the start, or else chronic, and it is a question how long one must keep them under observation. Relapses are common, but in the great majority of cases if the patients are carefully questioned they are found to be re-infections.

Two points which I discovered in the case of women were, firstly, being much more prone to headache and sickness they complain of the toxicity of sulphapyridine (M & B 693). Secondly, the G.C.F. test is essential, a test for cure in women being in most cases positive at the commencement of the treatment.

The following are cases of gonorrhoea in women treated by sulphapyridine (M & B 693) which seem of interest.

Case 1

A Housewife, a married woman aged 43, came to the clinic on the 2nd February 1939. On examination there was no urethral discharge but the cervical smear was G.C.† and the G.C.F. strongly positive. She was given M & B 693, 1 tablet 4 times a day, and/

and also vaginal irrigation. On reporting on the 6th February, she stated that she had had severe headache and vomiting but had taken all the tablets. There was no urethral discharge but some vaginal discharge. All clinical signs disappeared on the 13th February and the smears were negative. On the 2nd March she was clinically free and the smears still negative but the G.C.F. was positive. It was still positive on the 30th March and she was told to report in 2 months' time for a blood test. On the 22nd May the G.C.F. was negative and there were no clinical signs. She was discharged cured.

Comment A female patient with a positive smear and a strongly positive G.C.F. In four months the smears were negative and the G.C.F. brought down from strongly positive to positive and negative by sulphapyridine.

Case 2

A Shop Girl, unmarried aged 19, reported at the clinic on the 1st December 1938. On examination, smears from the urethra and cervix were G.C.+ and G.C.F.++ She was douched daily at the clinic and given sulphapyridine, 1 gramme 3 times a day for 5 days. She complained of slight headache. The clinical signs disappeared on the 22nd January 1939 and there was no recurrence. The G.C.F. was negative on the 29th January when she discharged herself.

Comment A young girl with positive smears and positive G.C.F. who was presumably cured in two months by sulphapyridine (M & B 693).

I will give in tabular form the next three cases.

Case 3

<u>Sex</u>	<u>Age</u>	<u>1st Attendance</u>	<u>Treatment</u>	<u>G.C.F. Test</u>	<u>Result</u>
3 Female	32	13.3.39	M & B 693 2 gms Smears-urethra daily for G.C.+ 7 days Smears-cervix G.C.-	+13.3.39 -25.8.39 Smears negative 25.8.39	Dis- charged 25.8.39

Case 4

4 Female	29	17.2.38	Sulphan- ilamide Smears-urethra 1 gm t.i.d G.C.+ for 2 wks Smears-cervix 5 gms t.i.d G.C.+ for 1 wk X	+17.2.38 -28.3.38 Smears- 28.3.38	Dis- charged 28.3.38
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Case 5

5 Female	24	15.12.38	M & B 693 2 gms daily for 5 days	+15.12.38 -23. 2.39 Smears- 23.2.39	Dis- charged 23.2.39
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Comments I have given these three cases as examples where under treatment with sulphanilamides a favourable result was obtained and the patient cured. There were numerous others, however, some with complications, who attended for months or discharged themselves without certain cure.

S U M M A R Y.

I have endeavoured by referring to old and new cases, over 200 in all dating from the beginning of 1937 to September 1940, to show how the sulphanilamides have improved the treatment of gonorrhoea in the male and to a lesser extent in the female. I have used sulphanilamide and sulphapyridine (M & B 693) and in a few cases sulphathiazole (M & B 760). Between the first two there is not much to choose, both being potent drugs. I have not had sufficient time to judge the possibilities of sulphathiazole. Sulphapyridine (M & B 693) is more rapid in its action than the sulphanilamides, and a lower dosage is used for a shorter time. It is also excreted more slowly. Sulphathiazole (M & B 760) seems in larger doses to be non-toxic, and is equally potent. In the majority of cases treated with sulphapyridine (M & B 693) the discharge ceased in twenty-four hours and the risk of complication is therefore almost nil. Relapses are to a great extent due to drug resistance where patients have previously been treated by inadequate doses. McLean, Rogers, and Fleming³³ have proved that pneumococci in mice treated with sulphapyridine (M & B 693) established a tolerance to the drug, and they stated that the initial dose should be large. Laboratory experiments³⁴ by Westphal and Carpenter say that gonococci have been/

been successfully sub-cultured on media containing increasing strengths of a sulphonamide compound and have shown that drug resistance can be acquired "in vitro." In my series 20% of relapses after sulphanylamide and 10% after sulphapyridine (M & B 693) were mostly due to drug resistance. Cokkinis and McElligott³⁵ reported that 20% of their 1,268 males and 210 females relapsed, and other letters in subsequent numbers of the B.M.J. agreed with them. In their cases there were 154 which did not have a G.C.t. smear and these may have been non-venereal which relapse more easily with sulphapyridine (M & B 693). I have found in my series that 3 grammes of sulphapyridine daily for 5 days, 15 grammes in all, in early uncomplicated cases clears up the discharge, and if the patients attend regularly for five successive weeks for tests for cure and observation, they can be discharged as cured. I get them to irrigate at the start, though I doubt if this is really necessary. The psychological value of treating the disease, apart from a box of tablets, is I am sure important to the patient. This may seem a short time to some research workers but my feeling is that if the drug is effective in twenty-four hours and cures in one week, surely five weeks of tests is long enough if a case is going to relapse. In this, however, I differ from other venereologists.

Batchelor/

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Batchelor, Lees and Thompson advise three months before discharging as cured. After the same dosage their figures for cures were 54% with sulphanilamide and 47% with sulphapyridine (M & B 693), which compare very much with mine of 43% and 50%. With their longer observation period my defaulters are less, 30% for both, while they have 46% and 53%. But if we add my apparent cures, 26% and 20%, this brings them more equal, 56% and 50%.

I note the Army Authorities have lately extended their period of observation from one month to three months for gonorrhoea and the R.A.F. six months, so it would seem that they have been having relapses with sulphapyridine (M & B 693). Looking at days under treatment my figures with irrigation average 75 days, with sulphanilamide 55 days, and with sulphapyridine (M & B 693) 52 days for 60 cases. In my latest series, however, the latter reads 41 days with sulphapyridine for 25 cases. MacKinnon found with irrigation that he cured his patients in 48 days, with sulphapyridine (M & B 693) 21 days, but his standard of cure is not stated. Somerville used much smaller doses. He used 1 tablet 4 times a day (2 gms) and obtained an early cure in 90% of cases, but he gives no indication of late relapses and tests for cure and it would be of interest to know his results. He mentions/

mentions a point I also found in my series, namely, that it did not seem to matter how long a time had elapsed since the onset of the disease before first treating the patient with sulphapyridine (M & B 693). The smear becomes G.C.-- just as quickly.

I think I have established that an early uncomplicated case of male gonorrhoea treated adequately with sulphapyridine (M & B 693) who attends regularly should be capable of being discharged cured in 35 days.^x The danger with the sulphanilamides I am sure is that owing to their almost dramatic effects the patient treated by his own practitioner with a box of tablets without adequate instruction and period of observation and tests for cure may quite easily relapse and then bring disrepute on a treatment that in capable hands is a very distinct advance in medical history.

Finally, I must thank A.C.B. McMurtrie, M.D., F.R.C.S.E. who allowed me to do this work at his clinic at the Cumberland Infirmary.

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C O N C L U S I O N S

Sulphanilamide, sulphapyridine and sulphathiazole are exceedingly potent drugs in the treatment of gonorrhoea, and there is not much to choose between them in the matter of cure.

Toxic effects were frequent but were never severe. They were much more marked with sulphapyridine, especially in the female, but we seem to have found the solution to this in sulphathiazole. All cases need observation and strict instructions how to take the drug in order to secure the maximum benefit. It is not enough to give a box of tablets, promise cure, and neglect tests for cure. Relapses occurred in the majority of cases after inadequate doses given by the patients' private practitioners, and no good results can be obtained by using the sulphanilamides again in adequate doses until the patient loses his drug resistance which takes about fourteen days. Sulphapyridine should in an uncomplicated case dry up discharge in twenty-four hours. If it fails to do so, suspect complication.

The Gonococcal Complement Fixation test in the male is of importance as a test in doubtful clinical cases without a positive smear, and in the female as a test for cure. Early cases under treatment with sulphapyridine (M & B 693) however, never become positive.

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