

THE SULPHANILAMIDES

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The parent substance of the drugs of this group is sulph-anilamide or, to give it its correct chemical name, para-aminobenzene-sulphonamide. From this compound many hundreds of derivatives have been prepared, only a few of which possess any therapeutic action. Actually about a dozen are employed in medicine, and unfortunately for both nurse and doctor they are marketed by commercial firms under a variety of trade names. This has led to considerable confusion. Here is a list of the more important ones together with their registered trade marks.

Sulphanilamide. Also known as prontosil album, streptocide, sulphonamide-p, colsulanyde, prontylin, rubiazol-a. This is the original preparation. It is quite useless to change from one of these preparations to another if the desired effect is not obtained with one and one wishes to try another sulphanilamide preparation.

M. & B. 693. So called from the initials of the manufacturing firm, who also call it Dagenan, from Dagenham, the site of their factory. It is also known as sulphapyridine (sulfapyridine in America), a corruption of its chemical name, 2-sulphanilylaminopyridine. It is available in the form of tablets, but a soluble form for injection, *M. & B. 693 soluble*, or Dagenan Sodium, can also be obtained in ampoule form. *M. & B. 693* is specific in pneumococcal infections.

Prontosil soluble is a five per cent. solution of a complex compound derived from sulphanilamide and naphthalene, a constituent of coal-tar. Being soluble it can be injected (intramuscularly). It is also known as prontosil, prontosil-S, prontosil-II, neoprontosil and rubiasol injectable. It is as active as sulphanilamide itself.

Prontosil rubrum, also known as prontosil flavum and sulphamido-chrysodin, is given orally. It has also been used dissolved in equal quantities of alcohol and acetone for cutaneous application.

Proseptasine, or benzylsulphanilamide, is also known as *M. & B. 125*. Being insoluble it can only be taken by mouth.

Soluseptasine, or *M. & B. 137*, is soluble and can be injected by intravenous, intramuscular, subcutaneous or intrathecal routes. An ointment is also available for the treatment of streptococcal infections of the skin or mucous surfaces. It is less active but also less toxic than sulphanilamide itself.

Albucid, an acetyl derivative of sulphonamide, is more specific for gonococcal than streptococcal infections.

Uleron (uliron in U.S.A.) has been used for gonococcal and staphylococcal infections.

Rubiazol, a French preparation, is a soluble sodium compound and can be injected intramuscularly. It is slightly less active, but certainly less toxic, than sulphanilamide.

Sulphathiazole is another new sulphanilamide preparation that has recently been tried out, especially in America. It is said to be less toxic than the other sulphanilamides. Therapeutic trials are still in progress.



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The sulphanilamides are highly specific in their action and cannot be used indiscriminately for the treatment of any infection. Their effectiveness in the treatment of many diseases has in some cases led to neglect of routine examination. Thus if a patient has earache one should not jump to the conclusion that there is a streptococcal infection of the middle ear and prescribe sulphanilamide without a careful examination. The writer has heard of a case in which the patient was cyanosed from overdosage with sulphanilamide, given for supposed otitis media, while his only trouble was an impacted wisdom tooth, causing referred pain in the region of the ear. The danger of sulphanilamide therapy lies in the masking of signs and symptoms. In this connection an American story of a conversation between two interns is worth repeating. "We'll give sulphanilamide to all admissions, and if they're not cured in three days, then we'll make a clinical examination."

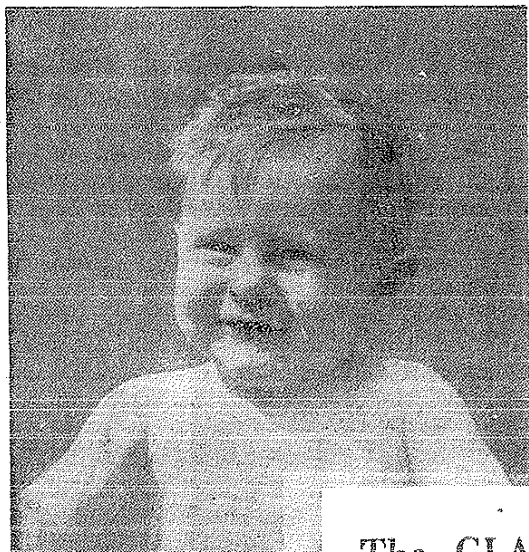
Broadly speaking the sulphonamides are effective in the treatment of *acute* infections due to certain strains of haemolytic streptococci (β -strains), pneumococci, meningococci, and bacillus coli. As a rule chronic infections are not so amenable to treatment. The compounds are inactive when the bacteria are in a medium full of pus. Thus it is useless to treat a suppurating cervical gland or an empyema with sulphanilamide without surgical treatment, although once this has been given the drug may be used as an adjuvant to treatment.

Streptococcal infections. The streptococcal infections in which the sulphanilamides have proved to be of value are: cellulitis, septicaemia, puerperal sepsis, otitis media, erysipelas, acute tonsillitis, meningitis (streptococcal), and scarlet fever (with streptococcus antitoxin).

In streptococcal cases the best preparations are considered to be sulphanilamide itself, prontosil rubrum, rubiazol, and, if the patient is unable to swallow or vomits, prontosil soluble (by injection). M. & B. 693 is undoubtedly active, but there is no evidence to show that it is any better than the cheaper sulphanilamide in combating streptococcal infections.

Meningococcal meningitis (cerebrospinal fever). For many years this has ranked as one of the most lethal of epidemic diseases, the case mortality being of the order of 30-50 per cent. This has been reduced to under 10 per cent. by sulphanilamide therapy. The drugs that have been most generally employed are sulphanilamide, proseptasine, M. & B. 693, and soluseptasine. Meningitis can also be caused by tubercle bacilli, streptococci and pneumococci. Owing to the fact that M. & B. 693 is effective against all these organisms (except tubercle), and that at the bedside the physician just diagnoses "meningitis" and not the causal organism, M. & B. 693 should be given in preference to the other preparations.

Pneumococcal infections. The pneumococcus can be the cause of lobar and broncho-pneumonia (usually a mixed infection), meningitis, peritonitis, otitis media and septicaemia. The most



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satisfactory drug for the treatment of these diseases is M. & B. 693. Since its introduction the prognosis in lobar pneumonia and in pneumococcal meningitis has improved considerably,

Gonococcal infections. The preparations that have found most favour are sulphanilamide, M. & B. 693, and uleoron. The last is only given for short periods of four days as it is only eliminated slowly. Cure is produced in about 80-90 per cent. of cases.

Bacillus coli infections. These include pyelitis, urinary infections, and the genito-urinary infections of childhood.

Other conditions. Reports on the value of M. & B. 693 and the sulphanilamides in a number of conditions are to be found in the medical journals. These include trachoma, gas gangrene, osteomyelitis, undulant fever, prophylaxis of wound infection (local and oral treatment), endocarditis, typhoid, infective skin conditions, and malaria. Although the sulphanilamides have not yet found a place in the treatment of the commoner infectious fevers (except scarlet fever), there is some evidence that they reduce the occurrence and severity of complications.

The actual manner in which the sulphanilamides restrain the activity of bacteria in the body is unknown. It is certain that they do not act as antiseptics, *i.e.*, they do not act by destroying the bacteria or inhibiting their reproduction. Nor do they increase the defence mechanisms of the body by increasing the number of white blood cells, or by stimulating the power of the latter to engulf and digest the bacteria. A most likely explanation is that the sulphanilamides act by preventing the bacteria from using proteins and other substances in human tissues as sources of nutriment. They thus become an easy prey for the attacking white blood cells.

It is necessary to point out four errors that commonly occur during the use of the sulphanilamides.

(1) *Sulphanilamides should not be given as a "shot gun" treatment on insufficient clinical evidence.* After clinical examination has led to a diagnosis the causal organism should be identified, if possible, by bacteriological methods so that the appropriate preparation may be used. Thus in pneumococcal infections M. & B. 693 should always be used in preference. On account of its wide range of usefulness this should also be employed if sulphanilamide therapy is instituted before a bacteriological diagnosis is made.

(2) *Do not neglect other methods of treatment.* A case of pneumonia requires careful nursing, besides M. & B. 693 every four hours. It may also be pointed out that in the treatment of streptococcal meningitis better results are obtained by the use of serum and a sulphanilamide preparation, than by the latter alone. In septicaemic cases blood transfusions may also be needed in addition to sulphanilamide.

(3) *Make sure that the drug is given early and that the dosage is sufficiently high.* To be effective, sulphanilamide must be given early during the course of infection, and it must be given in sufficiently high dosage to obtain and maintain a sufficiently effective concentration in the blood. For this reason initial doses



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are high, and, owing to the rapid excretion, maintenance doses must be given every four hours to keep the level in the blood high. In acute cases it is generally considered that adults should receive a maintenance dose of one gram every four hours.

(4) *A watch must be kept for toxic reactions.* These reactions, their avoidance and treatment are discussed later.

The dosage and preparation used will depend upon the nature and severity of the infection, the age of the patient, his condition, and the stage of the disease.

Streptococcal infections. Sulphanilamide or prontosil rubrum is given in doses of three tablets (of $7\frac{1}{2}$ gr. or $\frac{1}{2}$ gm.) followed by two tablets four-hourly, both night and day. This dosage should be maintained even after the temperature has fallen and should be continued for a week or longer. As clinical improvement sets in, smaller doses of one tablet may be given every six hours. It is generally agreed that after a fortnight treatment should be stopped for a day or two and then resumed again if necessary.

Children between 10 and 14 tolerate an initial dose of two tablets and a maintenance dose of one and a half tablets four-hourly. Between five and ten an initial dose of one and a half tablets is given, and then one tablet four-hourly. For smaller children the less toxic proseptasine or rubiazol may be employed.

Meningitis. The selected preparation should be given in large doses for the first two or three days.

Age in years:	Under 1	Under 2	Under 5	Under 10	Over 10
Dose in grams p.d.:	3	$4\frac{1}{2}$	6	$7\frac{1}{2}$	9

Initially a large dose should be given, and further quantities every four hours. Treatment is continued until the temperature has been normal for a week.

Pneumococcal infections. Severely ill patients, or those in whom the disease is well established, should receive initially four tablets (two grams) of M. & B. 693, followed by another four tablets four hours later. Thereafter two tablets should be given four-hourly for 36 hours. With clinical improvement the dosage may be reduced to one tablet four-hourly for another 24 or 36 hours, finally giving one tablet eight-hourly for two days. In less severe cases, after an initial dose of four tablets, four-hourly administration of two tablets may be begun. In the case of children the following scheme can be used.

Age:	...	...	1 to 3 months.	6 months to 2 yrs.	3 yrs.	5 yrs.
Dose in grams every four hours	0.125	0.25	0.375	0.5		

Gonococcal infections. An average scheme for an adult man is three grams of M. & B. 693 daily in divided doses for five days, followed by two grams daily for an additional five to nine days. For women the dose is slightly less, e.g., two grams daily to begin with. In young girls a five-day course of 0.25 to 0.5 gram four times daily is given.

The commonest toxic effects that may follow sulphanilamide therapy are malaise, headache, dizziness, nausea, anorexia, vomiting, "drug rash" of a morbilliform or urticarial nature, and "drug fever".

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The last occurs about the seventh to tenth day, and may cause some alarm if mistaken for a return of the infection. Cyanosis is common but not necessarily serious. More serious complications, fortunately not common, are haematuria, anuria due to blockage of the kidney tubules ("sulphanilamide stones"), and agranulocytosis.

The administration of sulphonamides should always be preceded by an ordinary soap and water enema and the bowel subsequently regulated with paraffin. Saline laxatives, liquorice powder, Epsom and Glauber salts, and severe purging must be avoided. Foods containing sulphur, such as eggs, onions and garlic, should not be eaten. Analgesics containing amidopyrin, phenacetin or phenazone are contra-indicated; so is Dover's powder, which may cause nausea. Adequate intake of fluids will minimise the occurrence of anuria and haematuria.

Sunbathing and exposure to ultra-violet light should be prohibited, owing to the risk of the drug making the patient photosensitive and causing drug dermatitis. Sulphanilamides should not be given to severely anaemic patients, and their use should be restricted when gross liver or kidney disease is present.

If mild cyanosis occurs it can often be relieved by administering methylene blue in pill form, one to two gr. t.d.s. A change to rubiazol, which is less toxic, may lead to improvement. Agranulocytosis demands instant treatment. The administration of sulphanilamide must be stopped, blood transfusions given, and pentnucleotide injected in doses of 10 c.c. up to three times a day. The dose is reduced to 10 c.c. once a day as the number of white blood cells rises.

Vomiting may prove so troublesome that an injectable form of sulphanilamide, e.g., M. & B. 693 sodium, or soluseptasine, has to be given. It can sometimes be overcome by giving the tablets crushed in milk with 15 gr. of sodium bicarbonate and $\frac{1}{2}$ dr. glucose. In cases of severe vomiting the use of intravenous saline should be borne in mind.

Quite recently it has been shown that the toxic effects of the sulphanilamides can be prevented, or at any rate relieved, by the simultaneous administration of vitamin C. In a Geneva clinic, daily intravenous injections of 0.5 gram are given to all patients receiving sulphanilamides, and it is claimed that toxic reactions are rarely seen. In America it has been found that nicotinic acid, given in doses of 20 to 100 mg. by mouth four times a day, is also effective in relieving the toxic symptoms.

By courtesy of *The Nursing Times*

A most uncritical wave of enthusiasm [for sulphonamide] is at present sweeping over town and country practice alike, and it is rare indeed for any patient who has a persistent sore throat, any prolonged elevation of temperature, or any obvious infection—wherein, however, the causal organism is not determined—to escape at least a dose or two of some sulphonamide preparation. It is said in defence that such a practice is relatively harmless compared with allowing a free hand to the streptococcus. The patients are, however, exposed to the toxic effect of the drug, there is a tendency to delay further investigations which might determine the etiological factors, and sometimes the treatment really appropriate to the condition is withheld.—
W. R. Snodgrass, M.D., B.Sc., F.R.F.P.S., writing in *The Practitioner*.