MEMORANDUM CONCERNING THE USE OF SULPHONAMIDE DERIVATIVES.

This memorandum supersedes all previous memoranda on this subject. It has been extended to include the treatment of the commoner infections known to respond to this group of drugs.

We have deleted certain paragraphs from the Memorandum as issued by the War Office (Editor).

PREAMBLE: Experimental and clinical results having proved the effectiveness of sulphonamide derivatives in the treatment of infections with hæmolytic streptococci, meningococci, gonococci, pneumococci, and B. coli, and, having indicated that these compounds have also an action on some, at least, of the anaerobic gas-forming bacilli, it is of importance for the medical officer to have knowledge of:

(1) The designation of the various compounds in use and the choice of compound.

(2) The principles governing the administration of these drugs both for prophylaxis and treatment.

(3) The toxic reactions to which the drugs give rise and how these may be avoided or treated.

This memorandum sets out the above general facts and makes particular recommendations for:

(A) The prophylaxis and treatment of wound infections due to streptococci and gas gangrene bacilli.

(B) The treatment of meningococcal infections.

(c) The treatment of pneumococcal infections.

DESIGNATION OF SULPHONAMIDE COMPOUNDS AND CHOICE OF COMPOUND.

Sulphanilamide: Synonyms: Sulphonamide P, Prontosil album; Streptocide, Colsulanyde. In France: Septoplix, Neococcyyl. Supplied in tablets of 0.5 g.

Sulphapyridine: Synonyms: M & B 693, Dagenan. Supplied in tablets of 0.5 g.

Sulphapyridine soluble: Synonyms: M & B 693 soluble, Dagenan sodium. Supplied as 33 per cent. solution. 1 g. in 3 c.c.

Sulphathiazole: Provisional name. Market supplies not yet available.

It is recommended that sulphapyridine should be exhibited in the following conditions: Gonorrhoea, cerebrospinal meningitis, pneumonia and pneumococcal infections, staphylococcal septicaemia, gas gangrene.

Sulphanilamide should be the drug of choice in the prophylaxis of wound infections and the treatment of erysipelas and cellulitis, meningococcal
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carriers, wounds known to be infected with haemolytic streptococci (acute phase), follicular tonsillitis and otitis media, B. coli urinary infections.

Note.—Sulphanilamide is inactive against all pneumococci with the exception of Type III and has but little action on staphylococci.

PRINCIPLES GOVERNING ADMINISTRATION OF SULPHONAMIDE DRUGS FOR PROPHYLAXIS AND TREATMENT.

The principle of effective treatment is to obtain a high blood concentration of the drug as rapidly as possible and to maintain this concentration at an effective level over a period of time. Because the drugs are rapidly excreted it is necessary, in order to maintain an effective level, to administer four-hourly night and day. The oral route of administration is best for maintaining a steady blood concentration and no other route should ordinarily be employed for treatment. There are occasions on which a soluble preparation for injection is of great value, such as when swallowing is impossible, when gastric upset prevents absorption, and in neglected cases in which it is imperative to lose no time in obtaining an effective blood concentration. A continuous course of a soluble preparation should only be used when oral therapy is impracticable. Courses of treatment for established or developing infections should very seldom exceed ten days. A further course should not be prescribed except in special circumstances and with adequate precautions against agranulocytosis. As a general rule when an infection is susceptible to the action of these drugs the result is rapid when they are administered in full doses.

When an infection appears to be controlled, as judged by the temperature, small doses should be continued for a further two to four days in order to prevent relapses.

TOXIC REACTIONS.

Certain individuals are unduly sensitive to the drugs and toxic reactions are liable to be caused by prolonged courses, repeated courses, and grossly excessive doses. When toxic symptoms are severe the drugs may be quickly washed out of the body by inducing simple diuresis with water.

The following is a list of the toxic reactions; the reactions may be classified as (i) mild, (ii) serious:

(i) Mild.

Nature of Reaction.—Vomiting: Especially common with sulphapyridine. Cyanosis: Cyanosis may be temporarily dispersed by giving 0.5 to 1.0 g. per day of methylene blue by the mouth. Cyanosis per se should not prohibit continuance of treatment. Acidosis. Drug fever: There is no certain means, apart from physical signs, of distinguishing this from fever due to recrudescence of infection. With true drug fever omission of the drug brings about an abrupt fall in temperature. Dermatitis: Omit drug and induce diuresis with water or simple diuretic. Check leucocyte count if
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possible. Dizziness, headache: If intolerable, administer fluids freely. Check leucocyte count if severe. Leucopenia: Negligible unless rapidly progressive to below 3,000 leucocytes per c.mm. Haematuria (sulphapyridine only): Administer fluids freely. Jaundice and neuritis: Omit drug. Induce diuresis. (See also Haemolytic anaemia.)

(ii) Serious.

Agranulocytosis: Occurs after eight days or more of treatment. Incidence rare. Leucocyte count (seventh day onward) only method of diagnosis. Other symptoms: headache, deterioration of condition, fever, sore or ulcerated throat. Treat: Abundant fluids, pentnucleotide 0·35 g. intramuscularly twice daily, transfusion of fresh defibrinated blood and preferably from donor who has had pentnucleotide four to five hours before. Haemolytic anaemia: Occurs early (two to four days). Incidence rare. Mortality low. Early signs jaundice and haemoglobinuria. Omit drug, induce diuresis, transfuse if necessary.

Prophylaxis and Treatment of Wound Infections Due to Streptococci and Gas Gangrene Bacilli.

For the time being it is recommended that a prophylactic course of sulphanilamide should be given to all wounded in whom there is reason to fear septic infection or gas gangrene. This should be started as early as possible (gas gangrene sometimes develops within the first six hours), and should be continued for at least four days in order to protect the patient against the risk of streptococcal infection contracted later in hospital.

Administration.

For prophylactic purposes it is recommended that the drug used should be sulphanilamide. Prophylactic treatment may be by oral administration or by local application to the wound. For the treatment of established infections either sulphanilamide or sulphapyridine may be used.

Prophylaxis.—(a) Oral: The first dose should be 1·5 g. (3 tablets) of sulphanilamide dissolved in hot citric acid or lemon in order to get rapid absorption. Subsequent doses, starting two hours later and continuing at four-hourly intervals for four days, should be 0·5 g. (1 tablet) as an uncrushed tablet in order to obtain delay in absorption. Dosage: First day, 4·5 g.; subsequent days, 3 g.; total, 13·5 g.

Note.—If the beginning of treatment has been unduly delayed or if the clinical condition gives reason to fear that gas gangrene is already beginning, the first two of the above doses should be doubled.

(b) Local application: The incorporation of 5 to 15 g. of powdered sulphanilamide into the depths of the wound at the time of débridement has been suggested as an alternative method of prophylactic treatment which may prove valuable, since the drug is readily absorbed from the wound into the blood stream and will also tend to check the development of bacteria.
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in and around the wound itself. The effects of such treatment must be observed, clinically and bacteriologically, on a selected group of cases before any decision is reached as to its wide application in war wounds.

Treatment: Sulphanilamide or Sulphapyridine.-(a) For gas gangrene and very severe streptococcal infections: The first dose should be 2 g. (4 tablets) dissolved in hot citric acid solution or lemon. Subsequent doses, starting two hours later and continuing at four-hourly intervals for two days, should be 1 g. (2 tablets) uncrushed. After the first two days the dosage should be gradually reduced as the clinical condition improves, but the interval between doses should not be more than six hours for several days. Small doses, e.g. 3 g. per diem, should be continued for three or four days after the temperature has come to normal and the clinical condition has become satisfactory. The duration of treatment and the total dosage will vary somewhat, but the latter should seldom exceed 35 g.

(b) For streptococcal infections of moderate severity: Dosage as for (a), but the total dose in the first forty-eight hours need not exceed 6 g. each day; sometimes 4 g. will be enough.

Note.—Hæmolytic streptococci (and possibly also gas gangrene bacilli) will sometimes persist in a wound long after the clinical condition has become satisfactory. Chemotherapeutic drugs should not be continued for this reason. It will seldom be advisable to prolong the treatment of wound infections beyond nine or ten days.

The Treatment of Meningococcal Infections.

Groups I and II meningococci are equally susceptible to the sulphonamide derivatives. The combination of antiserum and chemotherapeutic agents does not appear to influence the course of the disease. If serum is used it should be given intravenously or intramuscularly and not into the theca.

(a) Routine Treatment.—Either sulphanilamide or sulphapyridine may be used, but the latter is slightly more effective and has the advantage of being active against pneumococci as well as streptococci and meningococci.

The total dosage during twenty-four hours should be 8 g. and in extreme cases up to a maximum of 10 g. The spacing of the dosage is important. The compound should be given four-hourly night and day. At the beginning of treatment half the total twenty-four hour dose should be given during the first two administrations. After these initial administrations, the twenty-four hour dose should be divided so that an equal amount of the drug is administered every four hours. This procedure should be continued for two and a half to three days, and then the dose gradually reduced over the next six days to 2 or 3 g. per diem. It is important that the administration should not be interrupted. To prevent recurrence of infection administration should continue for some days after the disappearance of clinical symptoms, but normally the total period need not exceed nine days.

(b) Special Treatment.—Fulminating cases: The onset may be extremely rapid, and it is essential, therefore, that the optimum blood concentration
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of the drug should be attained at the earliest possible moment. The first dose should consist of two injections given simultaneously: an intravenous injection of 1 g. sulphapyridine soluble, diluted in three or more volumes of saline, and an intramuscular injection of 1 g. sulphapyridine soluble. The second dose should be an intramuscular injection of 1 g. sulphapyridine soluble four hours later. Subsequent doses must be judged by the condition of the patient. Dosage may be continued according to the scheme given above for cases of delayed diagnosis and treatment. Three or four pints of fluid daily should be given by whatever route is practicable, either oral, rectal, subcutaneous, or intravenous.

(c) Treatment of Carriers.—The following scheme has proved to be successful: 1 g. sulphanilamide is given by the mouth every eight hours and continued for six days, but not beyond this period. Local application of the drug has proved to be valueless.

The Treatment of Pneumococcal Infections.

Sulphapyridine must be used for the treatment of all pneumococcal infections. Sulphanilamide is inactive against all pneumococci with the exception of Type III.

Lobar Pneumonia.—For the treatment of lobar pneumonia the following dosage of sulphapyridine is suitable for the average case. 5 g. should be administered in the first twelve hours in lots of 2 g., 2 g., 1 g., four-hourly. This is followed by 1 g. four-hourly, six-hourly, or eight-hourly according to the response. The total dosage administered would be from 26 to 35 g. It is important that treatment should not cease immediately a crisis occurs, but should continue for at least forty-eight hours after the temperature becomes normal.

Should an empyema arise, it cannot be controlled or dispersed with sulphapyridine, though the drug may be used as an adjuvant to surgery.

The Treatment of Gonococcal Infection.

Chemotherapy should be employed in all cases in which there is no contraindication, such as previous intolerance, certain dermatoses and blood diseases, renal disease, jaundice and neuritis. Optimal dosage has not yet been settled, and the following recommendations may require modification with further experience.

(a) For Cases of Less than Ten Days' Duration.—Sulphapyridine is at present the most efficient preparation. The following scheme of dosage is suggested:

The tablets should be powdered and given in milk or water. 1st day of treatment: 2 g. at once and thereafter 0·5 g. every four hours during the day, and 2 g. at bedtime. 2nd day of treatment: 1 g. on rising, 0·5 g. after breakfast, dinner, tea and supper, and 1 g. at bedtime (total 4 g.). 3rd to
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7th day of treatment: 1 g. after breakfast, 0·5 g. after dinner and tea, and 1 g. at bedtime (total 3 g.).

If signs of urethritis persist longer than three days, treatment is continued at the rate of 3 g. a day for a further three days. Sulphapyridine should not be administered continuously for more than ten days at a time.

During the above treatment a milk diet is advisable for the first three days, and thereafter a light diet with avoidance of sulphur-containing food-stuffs.

(b) For Cases of More than Ten Days' Duration when First Seen.—Sulphanilamide appears to be as effective as sulphapyridine and is much cheaper. The dosage may be on lines similar to those suggested above, but 25–50 per cent higher.

The Treatment of Sundry Other Infections.

Staphylococcal Septicaemia.—Sulphapyridine is the most effective drug. The course required is similar to that described for lobar pneumonia.

It would appear from experimental evidence that the recently introduced compound sulphathiazole is superior to sulphapyridine in the treatment of staphylococcal infections.

Staphylococcal Pneumonia.—Staphylococcal pneumonia arises usually as a sequel to influenza. The mortality is high. Sulphapyridine appears to influence the infection in a proportion of cases and should be prescribed in the higher dosage recommended for pneumococcal pneumonia.

B. coli Urinary Infection.—Sulphanilamide should be used. An average course is 1 g. four-hourly for four to five days.
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