SULPHONAMIDE CHEMOTHERAPY

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(*Pharmaceutical Specialities (May and Baker) Ltd.*)

The publication by Domagk¹ in February 1935 of his findings that sulphonamido-chrysoïdin controlled experimental β -haemolytic streptococcal infections in mice may be said to be the beginning of sulphonamide chemotherapy. The next important step was the demonstration that sulphonamido-chrysoïdin, and allied sulphonamides containing an azo-dye, owed their activity to the release of sulphanilamide in the body. Sulphanilamide itself then came into widespread clinical use for the treatment of β -haemolytic streptococcal infections, *Bact. coli* infections of the urinary tract, and cerebrospinal fever.

The scope of sulphonamide therapy was greatly extended with the announcement in May 1938 that a derivative of sulphanilamide, known as "M. & B. 693," controlled experimental pneumococcal infections in mice, followed by a clinical report on the effectiveness of this compound in acute primary pneumonia. In the next year a pioneer paper by Jensen, Johnsrud and Nelson² appeared on the local implantation of sulphanilamide in compound fractures. The introduction of sulphapyridine led to many other heterocyclic derivatives being described in the literature, some of which have come into extensive clinical use. American investigators greatly extended our knowledge of the pharmacology of the sulphonamides and elaborated methods for their estimation in body fluids. The discovery of the specific inhibition of sulphonamide bacteriostasis by p -aminobenzoic acid led to the important theory expressed by Fildes³ that the sulphonamides and other antibacterial substances act by interfering with the essential metabolism of the organism. The investigation of this inhibitory effect by Woods⁴ and the demonstration by McIlwain⁵ that the bacterial enzyme-system could be blocked for several metabolites by structurally related compounds, added further to knowledge of this subject, and suggested that the synthesis of new antibacterial agents may in future be on rational rather than empirical lines. That substances inhibitory to the antibacterial action of the sulphonamides occur in pus, places unfortunate limitations on their clinical employment. Laboratory and clinical confirmation by British workers of a German claim that the activity of a sulphonamide of different chemical type called Marfanil, formerly known as Mesudin, is not inhibited by p -aminobenzoic acid or by pus, has led recently to the description of new compounds possessing this valuable property having a potent local chemotherapeutic action in gas

gangrene infections. The discovery of a compound having an anti-typhus activity suggests also that the chemotherapy of infections may extend to a field which has hitherto been outside the scope.

Compounds in Use

The original sulphonamides containing an azo-dye are now of historic interest only. They may be regarded as being derived from sulphanilamide by substitution in the amino (NH_2) group, and like them other compounds formed in this way owe their activity *in vivo* to the release of the parent substance. Certain colourless derivatives of sulphanilamide of this type are in clinical use and issued under the names "Soluseptasine," Sulphonamide EOS, and Sulphanilamide LSP. They are employed for parenteral administration and topical application, since these substances are much more soluble than sulphanilamide itself, and yield solutions which are approximately neutral in reaction. Of compounds formed by substitution in the sulphonamide (SO_2NH_2) group there are two open-chain compounds, sulphacetamide and sulphaguanidine, and a number of heterocyclic derivatives. The latter include sulphapyridine, sulphathiazole, sulphadiazine (not called sulphapyrimidine because this would be confused with sulphapyridine), sulphadimethylpyrimidine (known under the brand name "Sulphamezathine," and formerly called sulphamethazine), sulphamethylpyrimidine ("Sulphamerazine"), sulphapyrazine, sulphathiazoline, and others. All these compounds are of fairly low solubility in water; so for parenteral administration or topical application in solution, the sodium salts of sulphacetamide and of the heterocyclic derivatives are employed. Solutions of sodium sulphacetamide are neutral in reaction, but solutions of the sodium salts of the heterocyclic derivatives yield strongly alkaline solutions. The sodium salt of sulphanilamide itself is never used, nor is the sodium salt of sulphaguanidine employed, because this compound is given by oral administration for the treatment of intestinal infections only. There are two derivatives of sulphathiazole in clinical use formed by substitution in the amino group, succinylsulphathiazole ("Sulphasuxidine") and phthalylsulphathiazole ("Sulphathalidine"), both being employed for bacillary dysentery. Finally, it should be noted that sulphanilamide and its amide substituted derivatives are partly converted in the body into acetyl derivatives which are inactive, since the change takes place in the amino group. Thus sulphanilamide is partly changed into acetyl sulphanilamide, (not to be confused with sulphacetamide,) sulphaguanidine into acetyl sulphaguanidine, sulphapyridine into acetyl sulphapyridine, and so on.

Some of these names, such as sulphapyridine and sulphathiazole are officially recognised non-proprietary designations, whereas others, such as "Sulphamezathine," "Sulphasuxidine," and "Sulphathalidine," are proprietary names, i.e. names which are registered trade marks, or for which registration has been applied for, to indicate brands of the respective substances, and should not therefore be used as common names. The use of "sulpha" names as trade marks has introduced a new element of confusion into sulphonamide nomenclature. In writing of these compounds recognised common names should be employed, such as succinyl sulphathiazole and sulphadimethylpyrimidine in the absence of any shorter common name having official recognition. This has the additional advantage that such names as these indicate clearly the chemical nature of the substance.

Pharmacology

The action of sulphonamides is to interfere with the multiplication of susceptible bacteria, while not obstructing phagocytosis and the other defences of the body. For this purpose the drug must be present in sufficient concentration for a sufficient length of time. The optimum concentration will vary with the species and strain of the invading organism, the number of organisms present, the activity of the compound being used, and other factors. In general, the different sulphonamides have little specificity for bacterial species, the difference between them being quantitative rather than qualitative. Exposure of susceptible organisms to suboptimum concentrations either *in vivo* or *in vitro* may lead to the organisms acquiring a resistance to sulphonamide action, and this is not specific for the compound concerned. If a comparatively weak sulphonamide, such as sulphanilamide, induced a drug resistance, bacteriostasis might be secured by employing an adequate concentration of a much more active compound, such as sulphathiazole. Acquired resistance persists through many generations, the organism retaining this property when repeatedly passed through susceptible animals or subculture. The question of whether resistant strains are being produced by the treatment of patients is clearly one of great importance, and the possibility emphasises the desirability of avoiding the use of sulphonamides for the treatment of trivial infections and of using these drugs only when their employment is warranted, and then in adequate dosage and on correct lines. The development of sulphonamide resistance does not lessen the susceptibility of an organism to the antibacterial action of a compound of a different type, such as

penicillin, acridine antiseptics, (e.g. proflavine) or propamidine.

The inhibitory action on sulphonamide bacteriostasis of *p*-aminobenzoic acid extends to derivatives of this compound, including a number of local anaesthetics, such as procaine. The extent to which the use of these compounds would interfere with the therapeutic effect of a sulphonamide depends on a number of variable factors, but in general it is inadvisable to give injections of them to a patient receiving systemic sulphonamide therapy. When a sulphonamide is being employed topically it obviously must not be mixed with a local anaesthetic of this class. These anaesthetics also give the same colour reaction as sulphonamides in the methods used for the estimating of the latter, so their use should be avoided when obtaining samples of body fluids for the estimation of sulphonamide level.

After oral administration the absorption of sulphanilamide, sulphathiazole, sulphadimethylpyrimidine, and sulphamonomethylpyrimidine is rapid, peak blood levels being produced within two to four hours. The absorption of sulphapyridine and sulphadiazine is slower and more irregular, and may proceed over a period of six to eight hours. In the case of sulphaguanidine about two-thirds of the amount administered is usually absorbed, the remaining one-third being excreted in the faeces, although the degree of absorption may exceed this and is variable, depending on the dose administered and other factors. Where there is ulceration of the colon a high degree of absorption may occur. There is a common and quite mistaken impression that little absorption occurs with sulphaguanidine. This is true, however, of the succinyl and phthalyl derivatives of sulphathiazole as less than 5 per cent of the amount of these drugs administered is excreted in the urine. After absorption sulphanilamide is distributed fairly evenly throughout the body, but this is not the case with the heterocyclic derivatives, particularly sulphathiazole, owing to a high proportion of these compounds being bound to plasma albumin, and hence not free to diffuse through the blood-C.S.F. barrier. Because the concentration of sulphathiazole in the cerebrospinal fluid is low, American writers repeatedly state that this compound should not be used in the treatment of meningitis. As the meninges are highly vascular organs, an adequate concentration of a sulphonamide in the peripheral blood should ensure an adequate concentration at the site of infection. The passage of a sulphonamide into the cerebrospinal fluid is probably unimportant as regards the treatment of meningitis, and determinations of the concentration in the fluid during the treatment of meningitis are not required. Any estimations done to ensure adequate levels should be on the peripheral

blood. In actual practice sulphathiazole is found to be one of the most effective compounds for the treatment of cerebrospinal fever and other meningitides due to sulphonamide-susceptible organisms.

Sulphonamides are excreted almost entirely by the kidney, and the rate of excretion of sulphathiazole, sulphanilamide, sulphapyridine, sulphadiazine, sulphadimethylpyrimidine, and sulphamonomethylpyrimidine decreases in that order. This is of practical importance in respect of frequency of administration, as, in order to secure a fairly constant blood level, the more rapidly excreted drugs must be given at not less than four-hourly intervals, day and night, whereas the compounds excreted more slowly may be administered at less frequent intervals. The degree of acetylation is variable with the different compounds sulphathiazole, sulphadiazine, and the derivatives of the latter being usually acetylated to a less extent than sulphanilamide and sulphapyridine. On the average some 20 per cent of the compound in the blood is present in conjugated state, the proportion in the urine being higher, presumably on account of re-absorption of the free compound in the renal tubules or its slower excretion. Conversion into the inactive acetylated form takes place mainly in the liver and one of the many advantages of initiating therapy in grave infections by parenteral administration is that the peripheral blood conveying the drug to the lesion will have a higher proportion of the free compound compared to oral administration, following which the drug will pass directly to the portal circulation. Sulphonamides are excreted in most of the body fluids and pass into the foetal circulation. The amount which would be obtained by a suckling infant is quite insufficient for therapeutic effect, and moreover part is present in the inactive form. Equally no toxic effect is to be anticipated unless the infant has been sensitised during previous administration.

CLINICAL USE

Sulphonamides are most effective in infections running an acute course which tend to be generalised. In the treatment of such infections administration should be begun as early as possible with a high initial dose, commonly called the "*loading dose*," followed by a smaller dose given at regular, frequent intervals in order to maintain the blood concentration which has been secured at a fairly constant level. Administration should be for a short period only, *in general not beyond five to seven days*. In grave cases it is desirable to initiate treatment by parenteral administration. The frequency of subsequent oral administration depends on the rate of excretion of the compound being used and on the functional state of the

kidneys. The initial blood levels of the free compound considered desirable for severe infections are of the following order: sulphanilamide, 8-15; sulphapyridine, 5-10; sulphathiazole, 6-7; sulphadiazine, 8-15; sulphamonomethylpyrimidine, 8-15; and sulphadimethylpyrimidine, 8-15. Lower levels suffice for milder cases, and for prophylaxis still less is needed. No attempt should be made to restrict the fluid intake in order to obtain a higher blood level, on the contrary *the maintenance of an adequate fluid intake is essential*. The type of dosage used in grave infections for adults of average weight is three to four grammes intravenously with maintenance oral doses of 1.0 to 1.5 grammes until the temperature has been normal for two to three days. This dosage has to be varied with body weight, extent and severity of the infection, the sulphonamide sensitivity of the infecting organism, the stage of the infection at which treatment is begun, the state of the natural defences, the activity of the drug selected, the degree to which it is acetylated, the state of renal functioning, and other factors. Tables of dosage are therefore only a guide to assist the clinician in forming a judgment as to the dosage appropriate for the individual patient. It is important to bear in mind that *the greater the number of bacteria infecting the patient the higher the concentrations of sulphonamide required* (hence the importance of colony counts in blood-stream invasion), and that *the antibacterial effect is more efficient when the body temperature is raised*. The younger the patient the higher should be the dosage in proportion to body weight.

In some localised types of infection, such as those of the genito-urinary tract, a lower dosage suffices. The average dosage for acute adult gonorrhoea is four to five grammes of sulphathiazole or sulphadiazine daily for five days. Five grammes of sulphathiazole on each of two successive days, which has been recommended in official quarters, is *not* sufficient.

Juvenile vulvo-vaginitis is treated with 0.25 to 0.5 gramme four times daily for four days, followed by a second course of treatment after an interval of one week.

In ophthalmia neonatorum, gonococcal or non-gonococcal, 0.25 gramme should be the initial dose, followed by 0.125 gramme four-hourly for about five days.

Most urinary tract infections may be successfully treated with lower doses of two to four grammes daily, although a larger amount may be needed in severe or insensitive infections such as those due to *Staph. aureus*.

The dosage of sulphaguanidine in acute bacillary dysentery in adults may be three grammes three

to four times daily for three days, followed by three grammes twice daily for four days, with a higher initial dose in severe cases. American authorities recommend 0.05 gramme per kg of body weight every four hours, day and night, until the number of stools is five or less daily; then 0.05 gramme per kg. every eight hours for at least three days.

In children the dosage averages half that recommended for adults, and in gastroenteritis of the newborn 0.5 gramme four-hourly for mature and 0.25 gramme for premature infants has been recommended. *Milk should be withheld completely until the appetite returns, and it is essential to combat dehydration by maintaining a high fluid intake.* The dosage of succinyl sulphathiazole or phthalyl sulphathiazole can be rather less than that of sulphaguanidine, since they are more active.

The fundamental principles in sulphonamide therapy of early administration, high initial dosage, regular frequent maintenance dosage, and short course of treatment, apply to all acute infections. The necessity for observing these principles is less in subacute infections, and does not exist when chronic infective conditions are being treated. In some chronic conditions high initial dosage is positively dangerous, as in lupus erythematosus when acute exacerbation, accompanied by systemic disturbance, might be precipitated.

Sulphonamides are used in the treatment of infections by β -haemolytic streptococci of Lancefield's groups A and C, meningococci, gonococci, pneumococci, *Staph. aureus*, *Bact. coli*, *H. ducreyi*, *Cl. welchii*, and *Cl. septicum*. They are employed in bacillary dysentery for the treatment of the acute phase, the cure of the convalescent-carrier state, and the treatment of symptomless carriers. They are used in urinary tract infections by *Bact. coli*, *Staph. aureus*, and other organisms, are of limited value against *Ps. pyocyanea*, and *Proteus*, and are ineffective against the enterococcus (*Streptococcus faecalis*). Insusceptible strains of organisms normally susceptible may be encountered. Favourable results have been reported in cholera and plague. The combined effect of sulphonamides and penicillin on susceptible organisms *in vitro* is greater than either drug alone, and clinical reports have shown the greater effectiveness of such a combination in treating pneumococcal meningitis and gonococcal male urethritis. This suggests that when supplies of penicillin are limited, combined therapy will effect a saving in penicillin while securing an adequate therapeutic response. Such a combination would appear to be worth using in grave acute *Staph. aureus* infections where sulphathiazole or sulphadiazine alone are likely to be insufficiently effective, and where penicillin alone would be required in large amounts.

It is obviously unjustifiable to submit patients to a risk of toxicosis or the development of sensitisation by administering sulphonamides in acute infections due to insusceptible organisms for the treatment of which they cannot be effective. Nevertheless the temptation to "do something" for the patient by giving a sulphonamide in, for example, brucellosis, and publish the resulting "cure" seems irresistible to many clinicians.

There are a few chronic conditions of known and unknown aetiology in which sulphonamides are useful or even valuable, including actinomycosis, dermatitis herpetiformis, and lupus erythematosus. Their usefulness in pemphigus vulgaris or other forms of chronic pemphigus is limited. Claims that sulphapyridine has a value in dermatitis herpetiformis and pemphigus not possessed by the other heterocyclic derivatives are probably made on inadequate observation; if true, it is inexplicable. Cases of chronic urinary tract infections in which careful investigation has failed to reveal any obstruction usually relapse on withdrawal of the drug. The joy of sufferers from dermatitis herpetiformis at the striking relief of their distressing symptoms secured by a sulphonamide usually turns to disappointment when the drug is withdrawn. Cases of abdominal actinomycosis tend ultimately to relapse with involvement of the liver. In all such cases, after securing initial improvement, a small maintenance dose should be continued without intermission for months or, if necessary, years. These small doses are usually well tolerated, but such small risk of blood dyscrasia as there may be is justified. In chronic urinary tract infections as small a dose of sulphapyridine as 0.5 gramme every other day is sometimes sufficient to keep the bacilluria at bay.

Administration and Topical Application

The sulphonamides are administered orally, by intramuscular, intravenous and subcutaneous injection, by drip infusion into veins or subcutaneous tissues, rectally, and by direct application to wounds, skin, mucosae, peritoneal and thoracic cavities, aural canals, accessory nasal sinuses, conjunctivae, etc. *They should never be injected into the subarachnoid space.* The soluble neutral derivatives of sulphanilamide formed by amino-substitution and the sodium salt of sulphacetamide, may, if desired, be given by subcutaneous injection and used freely by topical application. The sodium salts of the heterocyclic derivatives yield solutions which are strongly alkaline, and should be given intravenously by injection or infusion. Deep intramuscular injection may be employed as an alternative provided precautions are taken to avoid contamination of the sub-

cutaneous tissues. A few cases of foot drop and wrist drop from damage to nerve structures have been reported in the literature, but a number of others have occurred, some resulting in legal complications. There is a tendency now to use the vastus externus and be on the safe side. While a concentrated solution is highly damaging to subcutaneous tissues a very dilute solution containing the equivalent of five grammes in 100 c.c. normal saline may be employed by hypodermoclysis, but absorption is slow and irregular. For intravenous injection a 5 per cent solution of the sodium salts in sterile distilled water is recommended, but a 10 per cent solution is frequently used. For intravenous infusion the required amount may be added to saline or glucose saline, but not to blood, plasma or serum. For intramuscular injection a concentrated solution is used containing the equivalent of one gramme in three or four c.c. The sodium salts should not be given rectally, and the heterocyclic derivatives themselves are but slightly absorbed from the rectum. Sulphanilamide has been administered by this route in the form of a saturated solution (approximately 0.8 per cent), or in suppositories, but the method is unsatisfactory as absorption is slow and blood levels inadequate. Sulphaguanidine is occasionally employed as a retention enema for a local effect in ulcerative colitis, seven to ten grammes in seven fluid ounces, water or mucilage being used.

For topical application to wounds or to the peritoneum sulphanilamide or sulphathiazole or a mixture of the two up to a maximum of 15 grammes is usually used. For the peritoneum sulphapyridine or sulphadiazine are not advised as, owing to their slow absorption, solid cakes may form, but Gardiner⁶ has not found sulphapyridine to cake or produce adhesions provided it is applied in a fluid suspension and not dry. His paper on intraperitoneal chemotherapy provides a valuable review of the subject in all its aspects.

For topical application in pyoderma sulphathiazole or sulphadiazine is generally used in the form of an ointment. Five per cent seems to be the optimum concentration of sulphathiazole for this purpose, and it is applied in the form of a stiff paste in preference to a cream.

Water-soluble creams are used in burns as well as dusting with the sulphonamide in powder form. For wound therapy sulphathiazole containing 1 per cent of proflavine sulphate has recently been recommended. The mixture is dusted over the surface of the wound by insufflator or sprinkler in an amount which is just sufficient to give a slight coating on the surface. This may be repeated after an interval of forty-eight hours. It was reported that irritation did not appear to occur provided the

application was not continued for too long. Nevertheless the sulphate of proflavine, which is the official salt in the pharmacopoeia, yields solutions which are strongly acid, a 1:1,000 solution having a pH of about 2.5, so that it is desirable in preparing this mixture to replace the official acid salt by one which is neutral in reaction. It is usual to sterilise sulphonamide powders, including the mixture with proflavine, before being issued or used.

For application to the eye solutions of sodium sulphacetamide are often used, since this yields neutral solutions unlike the sodium salts of the heterocyclic derivatives. An ointment containing 10 per cent of sulphathiazole in soft paraffin with a small proportion of cholesterol has been found useful in blepharitis of various clinical types, both acute and chronic.

The Sulphones

In 1937, Buttle, Stephenson, Smith, Dowling and Foster⁷ reported that 4:4' diaminodiphenylsulphone was active in curing streptococcal infections in mice in doses of about 1/100 of those required with sulphanilamide, and was about twenty-five times as toxic. It was not more toxic than sulphanilamide in normal rabbits or monkeys. It is considered that the toxicity of this compound probably precludes its clinical employment in man. Veterinary clinicians have found that therapeutic doses in cattle are of low toxicity. Various derivatives of 4:4' diaminodiphenylsulphone have been studied, and a number used clinically. These compounds are more effective than sulphonamides in retarding experimental tuberculous infections in guinea pigs, and their chief clinical interest lies in their use for treating tuberculosis, systemically or by topical application to accessible lesions. Derivatives of 4:4' diaminodiphenylsulphone concerning which reports have appeared are "Promin" (also known as "Promanide"), "Diasone," and "Promizole."

REACTIONS TO SULPHONAMIDES

Cyanosis of a transient nature, associated with methaemoglobincyaemia or, more persistently, associated with sulphaemoglobincyaemia, was common when sulphanilamide was the chief sulphonamide used, and attracted an unwarranted degree of attention. It is much less common with the heterocyclic derivatives, and when it occurs is often due to phenacetin, a proprietary or non-proprietary tablet of which with codeine and acetyl salicylic acid being much prescribed as an analgesic by the medical profession, and consumed with avidity by the laity, and frequently given to patients during sulphonamide therapy. Clinicians

tend to overlook the cyanosis-producing properties of phenacetin, and to blame the sulphonamide as a consequence. There is no objection to the use of acetyl salicylic acid or of the barbiturates during sulphonamide therapy, although proprietary preparations of a barbiturate with either phenacetin or amidopyrine should be avoided. The latter drug should never be given during sulphonamide therapy, even if its use is justified in patients not taking a sulphonamide, which is doubtful. The formation of sulphhaemoglobin is an irreversible reaction, and it persists for the life of the erythrocyte containing it, but methaemoglobincyaemia may be abolished, if desired, with methylene blue.

Symptoms of cerebral origin include *vomiting* and *nausea* and such mental effects as *depression*, *confusion*, *headache* and *excitement*. They are especially liable to occur with sulphapyridine, less common with sulphathiazole, and least common with sulphadiazine or its methyl derivatives. When they occur with sulphapyridine one of the other compounds should therefore be substituted. Small doses of a sedative such as phenobarbital may be useful in vomiting, since it is central and not local in origin, but persistent vomiting, whether due to drug or disease, usually requires parenteral administration in order to ensure adequate intake of the sulphonamide.

Sulphanilamide has an inhibitory action on the enzyme carbonic anhydrase and may produce *acidosis*, an effect which does not appear to occur with its heterocyclic derivatives, and which may be prevented or treated by alkalis.

Drug pyrexia generally precedes *drug rashes*, and occurs after about eight days of administration. These are due to sensitisation. There may be associated *conjunctivitis*, *lymph node enlargement*, *arthritis*, or *splenomegaly*. If a patient has been sensitised by previous administration, these effects may be produced within a few hours, so that enquiry regarding previous treatment is an important part of the patient's history before sulphonamide therapy is begun. By limiting administration to five to seven days the incidence of sensitisation is reduced, but even then symptomless sensitisation may occur. On the appearance of sensitisation symptoms, administration may be continued in reduced dosage to desensitise the patient. Rashes will then disappear more quickly, but administration must be continued for some time after the rash has disappeared in order to complete the process. Some consider that administration should be stopped on the appearance of symptoms and desensitization carried out after antibody formation has ceased. In all cases a test dose should be administered later. Sensitisation is common after local application to the skin, and these cases also can be desensitised by oral administration, for which

purpose a dose of 0.125 gramme twice a day has been found safe in most cases by Tate and Klorafin, although the optimum dose is highly individual. Sensitisation is usually nonspecific among different sulphonamides, but this is not always the case.

Leucopenia occurring early in administration, unless severe, is unimportant, and will not lead to agranulocytosis provided administration is not continued beyond the recommended period. The size of the individual doses and the total amount given are largely immaterial as regards the occurrence of agranulocytosis. Possibly the aetiology of sulphonamide agranulocytosis varies, but in most cases it appears to be due to sensitisation. The usual advice is to stop the drug, but it is better to continue in the hope of desensitising the patient, and of treating the mucous surface infection. When *agranulocytosis* occurs independently of sulphonamide administration, for example, due to a drug of different chemical nature, a sulphonamide may be given if desired for the treatment of infection resulting from the absence of phagocytes. Leucopenia instead of leucocytosis in an infection is no contraindication to sulphonamide therapy. In pneumococcal pneumonia with leucopenia, or such grave pre-sulphonamide prognosis, the indication would be for boldness and not timidity in sulphonamide dosage.

Mild anaemia from sulphonamides is unimportant, but *acute haemolytic anaemia* may progress rapidly, and when it occurs it does so early during administration. Owing to its being comparatively uncommon in this country, acute haemolytic anaemia as a cause of *jaundice* on the third day of sulphonamide administration has sometimes been overlooked. The mechanism of the condition being obscure, it cannot be stated whether or not the usual advice to stop the drug immediately is well founded. Fluids, alkalis, and blood transfusion are, of course, required. *Acute aplastic anaemia* and *thrombocytopenic purpura* are both rare. The latter appears to be due to sensitisation, as it is when caused by a number of other drugs.

Most of these phenomena are examples of conditioned toxicosis rather than direct toxicity, some form of individual idiosyncrasy, natural or acquired being involved. Excessive dosage or inadequate elimination may, however, cause direct toxic effects, and if there is doubt as to the aetiology of a reaction, determination of the blood or urine levels is required. A simple test which is roughly quantitative only may suffice for clinical purposes, carried out by diluting a little urine ten times and noting the depth of colour with a few drops of Ehrlich's reagent or Werner's modification of it. Urobilinogen gives Ehrlich's reaction, and the present might interfere, but it may be changed

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into urobilin by shaking with a few drops of hydrogen peroxide.

The concentration of the sulphonamide in the urine is with the usual dosage greater than its solubility. Like most supersaturated solutions, sudden crystallisation out is liable to occur, and this may take place in any part of the urinary tract. Prevention is by the maintenance of an adequate fluid intake and urinary output. The administration of alkalies in a dosage sufficient to keep the urine alkaline is of assistance in preventing crystalluria from sulphathiazole or sulphadiazine. When *oliguria*, *haematuria*, or *renal pain* occur the drug should be stopped and fluids forced, but persistent severe oliguria or the occurrence of persistent anuria calls for urethral catheterisation and irrigation of the renal pelvis with a warm 2.5 per cent solution of sodium bicarbonate. This complication is liable to occur with any of the heterocyclic derivatives, but is less likely with sulphadimethylpyrimidine. It has occurred with sulphaguanidine, although the possibility with this compound is much less. Sulphanilamide and sulphacetamide are virtually free from this danger.

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