RECENT WORK ON THE PHARMACOLOGY OF SULPHONAMIDES

BY

FRANK HAWKING, D.M.

National Institute for Medical Research, London

Under the heading of pharmacology it is convenient to consider all the actions of sulphonamide compounds on the body of the host, excluding the detailed discussion of the toxic symptoms encountered in clinical practice. On the whole, sulphonamides are rather inert from a pharmacological standpoint, and the greater part of any article on this aspect is necessarily occupied by a consideration of the factors involved in maintaining an optimal concentration at their site of action. The methods developed by Marshall and his colleagues for the estimation of sulphonamides in blood are too well known for consideration here. Bogen (1943) has described a simple method of testing urine to find if the patient has already received a sulphonamide. (A drop of urine is placed on wood-pulp paper—e.g., newspaper—and a drop of hydrochloric acid is added; with a sulphonamide a yellow colour appears.) Procaine (novocain) gives the same colour as sulphonamides in Marshall's test (which can thus be used for its estimation); consequently this and other local analgesics which contain the *p*-aminobenzoate group must not be used for the collection of specimens for sulphonamide estimations.

Absorption

When sulphonamides are taken by mouth they are rapidly absorbed. Apparently most of this absorption occurs in the upper part of the small intestine, but there is evidence suggesting that much may be absorbed through the stomach wall. Usually absorption is complete before the ileo-caecal valve is reached. Sulphanilamide and sulphathiazole are rapidly absorbed, sulphadiazine more slowly. The absorption of sulphapyridine is slower, less regular, and less complete than that of the other compounds (Kinsman, Moore, and Harrison, 1940). Absorption from the large intestine can occur, but the rate is slower (Turell, Marino, and Nerb, 1940; Marshall, Bratton, White, and Litchfield, 1940). In cases where oral administration is not possible—e.g., after operation on the stomach—sulphanilamide may be given per rectum, but the amount absorbed is always uncertain and the resulting blood levels tend to be low (Wood, 1941). Sulphapyridine and sulphadiazine are both poorly absorbed from the large intestine (Peterson, Strauss, Taylor, and Finland, 1941).

If the sulphonamide is given with an empty stomach it is absorbed slightly more quickly than if given after a meal; but the difference is not great enough to be of clinical importance or to compensate for the greater risk of nausea. Similarly the administration of acid or alkali at the same time as the sulphonamide does not appreciably alter the rate of absorption (Peterson and Finland, 1942; Wilson, 1943). When sulphapyridine, sulphathiazole, or sulphadiazine is given by tube direct into the duodenum, absorption may be greatly diminished, suggesting that a considerable portion of the sulphonamide may reach the blood stream through the stomach wall; this effect was not shown when sulphanilamide or sodium sulphadiazine was given (Peterson and Finland, 1942). Sodium sulphonamides have been suggested for oral administration in order to obtain rapid absorption, but their issue for this purpose has not received the approval of the Council on Pharmacy and Chemistry of the American Medical Association. It is claimed that the absorption of sulphanilamide can be accelerated by giving it as a solution with glucose, glycerin, and sodium lactate, or with sodium lactate and potassium citrate, but the difference is not great enough to be of clinical value (Siebert and Loose, 1940).

Sulphanilamide and the soluble preparations of the other sulphonamides are quickly absorbed when injected intramuscularly or subcutaneously. Absorption is of course most rapid (instantaneous) when the compound is injected intravenously. Absorption is also rapid from serous cavities, such as the peritoneum and pleura (Hawking and Hunt, 1942; Vickers, 1943), from large raw areas—e.g., burns—and from large wounds (depending on their size, shape, and vascularity); on the average, absorption from these sites is about half as rapid as from the alimentary canal.

Distribution

After absorption into the blood stream sulphanilamide diffuses through the whole body. In dogs, about 4 hours after an oral dose, the compound is distributed approximately evenly through all the tissues except bone and fat, and the concentration in the tissues is equal to that in the blood (Marshall, Emerson, and Cutting, 1937b). During the period preceding this phase of equilibrium the concentration in the blood is greater than that in the tissues; following this phase, the blood concentration is lower than the tissue concentration (Alexander, 1943). Although there is no tendency for the compound to be concentrated in any special tissue, some organs contain more than others. Thus during the first six hours (in rabbits), if the concentration in the blood is taken as 1.0, the average concentration in the liver is 1.2, in the kidney 2.0–3.6, in the brain about 0.6, and in muscle 0.8 (Alexander, 1943). According to some figures of Waterhouse and Shannon (1942) for dogs, if the concentration of sulphanilamide in the plasma is taken as 1.0, that in the erythrocytes is 1.4, in the lung 1.1, in the liver 1.3, in the pancreas 1.1, in muscle 1.1, in the cerebrospinal fluid and in the brain 0.6, and in nerves 0.76. In dogs no acetylation occurs and all the sulphanilamide is present in the free form. The distribution in the blood between the erythrocytes and the plasma differs somewhat with the different compounds. Thus if the concentration of the free form in the plasma is 1.0, that in the erythrocytes is:

Sulphanilamide ..	1.0–2.1	{ (Simesen, 1941a, 1941b; Reinhold, Flippin, Schwartz, and Domm, 1941; Ratish, Shackman, and Bullowa, 1942; Murphy, Clark, and Flippin, 1943)
Sulphapyridine ..	0.6–1.1	
Sulphathiazole ..	0.3–0.4	
Sulphadiazine ..	0.25–0.5	
Sulphamerazine ..	0.3	
Sulphacetamide ..	1.5	
Uleron ..	1.0	

Similarly as regards the penetration into the cerebrospinal fluid, if the concentration in the plasma is 1.0, that in the cerebrospinal fluid (when equilibrium is reached) is:

Sulphanilamide ..	0.7–1.0	{ (Marshall and Litchfield, 1939; Sadusk, Blake, and Seymour 1940; Banks, 1941; Long, 1941; Reinhold, Flippin, Schwartz, and Domm, 1941) (Macartney, Smith, Luxton, Ramsay, and Goldman, 1942) (Murphy, Clark, and Flippin, 1943)
Sulphapyridine ..	0.7	
Sulphathiazole ..	0.15–0.4	
Sulphadiazine ..	0.5–0.8	
Sulphadimethylpyrimidine ..	0.4–0.8	
Sulphamerazine ..	0.3–0.7	

(Probably the differences between the various compounds are due to the differing amounts "bound" to the plasma proteins; see below.) Actually the ratio (concentration in C.S.F./concentration in plasma) is lower than these figures during the earlier part of treatment, when the blood concentration is rising, and higher when administration of the drug is stopped and the blood concentration falls. Similarly, the concentration in peritoneal, pleural, and joint effusions tends to be somewhat lower than

that in plasma when equilibrium is reached; but there is a lag of 2-3 hours in arriving at this position (Cantarow, Cubberley, and Rakoff, 1942). The concentration of sulphathiazole in the fluid of infected or uninfected knee-joints is approximately the same as that in the blood (Heyl, 1941). As regards the eyes, when sulphanilamide is given to dogs the concentration in the aqueous humour one hour later is about 33% of that in the blood, rising to a maximum of about 61% four hours after administration (Bellows and Chinn, 1939); when 100 mg. sulphapyridine was applied locally to the conjunctiva (of rats) the concentration one hour later was 47 mg. per 100 c.cm. in the conjunctiva, 30 mg. in the cornea, and only 5 mg. in the aqueous humour (P'an, 1941). The content of sulphapyridine in the pancreatic juice (of cats) after its administration by mouth is slightly less than that of the blood (Taylor and Agren, 1940). [For bile, see under "Excretion."] Sulphanilamide is also found in menstrual blood; but in the normal secretion of the cervix uteri it is present in such small amounts that its bacteriostatic action is problematic.

The Foetus.—Sulphonamides pass through the placenta into the foetal circulation, and therefore there are possibilities of toxic and of therapeutic action. Speert (1943) recommends that in order to prevent bacterial invasion of the foetal blood vessels in cases of prolonged labour with ruptured membranes, and in cases where it is desired to protect the foetus against intrapartum infection by gonococci from the mother, the woman in labour should be given a single intravenous dose of 5 g. sodium sulphadiazine; during the next few hours concentrations of 9-11 mg. per 100 c.cm. will be maintained in the foetal blood and 10-20 mg. in the maternal blood. This procedure involves a possible (but low) risk of renal obstruction in the mother. Although prolonged treatment with sulphanilamide is injurious to the foetus (Adair, Hesseltine, and Hac, 1938; Speert, 1940), in animals or in human beings the danger from a single dose is probably small (Philipp, 1941).

Combination of Sulphonamides with Plasma Proteins.—Part of the sulphonamide in the plasma is bound in some way to the plasma proteins, and is not free to pass through a dialysis membrane. The combination with protein cannot be very strong, as sulphonamides are not precipitated to any large extent when the proteins of blood or serum are thrown down by trichloroacetic acid in the first stage of Marshall's quantitative test. The combination apparently involves the plasma albumin principally, while the globulin and lipoids are not concerned (Davis, 1942). The higher the concentration of sulphonamide, the smaller the percentage of bound drug; the figures below refer to blood concentrations of the therapeutic range (2-20 mg. per 100 c.cm.). The amount bound is approximately proportional to the amount of albumin present. The binding is not diminished by denaturation of the protein with ultra-violet light (Davis, 1943). Similarly, red prontosil is combined with the albumin of the serum but not with the globulin, as was shown by Schönholzer (1940), using a cataphoresis technique. The extent to which this binding occurs differs with the different compounds, as shown below (Davis, 1942; Heinemann, 1943):

Sulphanilamide		12-20% bound
Sulphapyridine		40-45% "
Sulphathiazole		75-80% "
Sulphadiazine		55-60% "

Compounds similar to the sulphonamides but lacking the *p*-amino group, and acetyl derivatives of sulphonamides, are bound to the proteins in the same way (Davis and Wood, 1942). Apparently the bound drug is not bacteriostatic, although, as the combination is loose, it forms a store of potential activity. The occurrence of this combination with protein probably explains the different distribution of the various compounds between plasma and erythrocytes, and between blood and cerebrospinal fluid, which have been described above. In fact, the calculated distribution between blood and a dialysate through a membrane permeable to sulphonamides, but not to protein, agrees closely with that observed clinically between blood and cerebrospinal fluid. Such combinations with proteins may conceivably play a part in the production of such sensitization phenomena as drug fever and specific skin sensitivity.

Metabolism of Sulphonamides

As is well known, much of the sulphonamide compound introduced into the body is conjugated, especially with acetate,

to form acetyl derivatives which are therapeutically inert, although equal in toxicity to the original sulphonamide. Sulphanilamide and sulphapyridine are more readily acetylated than sulphathiazole and sulphadiazine. On the average, about 20% of sulphanilamide in the blood and about 25-60% of that in the urine is in the conjugated state. With sulphapyridine, about 33% (10-45%) of the total compound in the blood and about half of that in the urine is acetylated in man (Kinsman, Moore, and Harrison, 1940). With sulphadiazine, the acetylated form accounts for about 10% of the compound in the blood and for about 25-33% of that in the urine (Peterson, Strauss, Taylor, and Finland, 1941). With sulphathiazole, about 20% of the compound in the blood is acetylated (Frisk, 1940a, 1940b), or 0-30% (average 12%) (Sadusk, Blake, and Seymour, 1940). The site of acetylation seems to be mostly in the liver (Harris and Klein, 1938), though in some animals other organs also can bring about this conjugation. Besides the sulphonamide inactivated by acetylation, there is evidence that part is combined with other compounds (especially glucuronic acid), or is degraded by other chemical processes. It has been shown by Simesen (1941a) that during the first day (in mice) up to 50% of the sulphanilamide may be destroyed in some way at present unknown, while 40-50% of sulphathiazole and of sulphacetamide is destroyed in this time; 40-50% of sulphapyridine is destroyed in 2-3 days, and 70% of uleron in 3-4 days. Alexander (1943) has confirmed this by giving sulphanilamide to mice and analysing the amount found in the excreta and in the (minced) body after various periods.

Excretion

i. Urine.—The main excretion of sulphonamides is through the kidney, the amounts passing out by other routes being comparatively insignificant. Part is excreted unchanged and part as the acetyl derivative, as has been described above. Apparently sulphanilamide passes out from the plasma into the glomerular filtrate and some of it is reabsorbed in the tubules. In dogs the sulphanilamide clearance is 20-30% of the creatinine clearance (only slight reabsorption in the tubules), so presumably 60-70% of the sulphanilamide in the glomerular filtrate is reabsorbed. The clearance is independent of the plasma level, but increases as the flow of urine is increased. In rabbits the clearance of the sulphanilamide is 30-40% that of creatinine and inulin, but the clearance of acetyl sulphanilamide is the same as that of these two compounds; presumably acetyl sulphanilamide is not reabsorbed in the tubules (Loomis, Hubbard, and Koepf, 1943). The average renal clearances in man for the original sulphonamides and their acetyl derivatives respectively are:

Sulphapyridine	..	23 and 58 c.cm. of plasma a minute
Sulphathiazole	..	43 " 55 " " " "
Sulphadiazine	..	31 " 59 " " " "

i.e., the amount of compound present in this volume of plasma is excreted by the kidney each minute.

As regards the proportion of the dose excreted in the urine various estimations have been given:

Sulphapyridine (usual clinical dosage): 60-90% (Frisk, 1940a), or about 30% (22-56%) (Kinsman, Moore, and Harrison, 1940), appears in the urine, about half being in the conjugated form.

Sulphathiazole: Daily excretion amounts to 75% of the intake (Simesen, 1941b), to 86-92% of the intake (Frisk, 1940b), or to 100% (Spink and Hansen, 1940).

Sulphadiazine: When 4-5 g. is given orally, 60% is excreted in urine in 24 hours, and 75% in 72 hours; a quarter to a third is in the conjugated form (Peterson, Strauss, *et al.*, 1941). Other data are given by Ratish, Shackman, and Bullowa (1942); Reinhold, Flippin, *et al.* (1941); and Sadusk, Blake, and Seymour (1940). When it is desired to increase the excretion of sulphadiazine (e.g., because of agranulocytosis) sodium bicarbonate should be given: to decrease the concentration in the urine (e.g., because of renal complications) large volumes of 5-10% glucose should be injected intravenously or much water may be given by mouth; intravenous injection of saline is less effective (Peterson, Goodwin, and Finland, 1943).

ii. Faeces.—The work of Marshall, Bratton, *et al.* (1940) on sulphaguanidine and the treatment of bacillary dysentery has directed attention to the amount of sulphonamide appearing in the faeces. Practically all such compound represents the portion which has not been absorbed during passage down the alimentary canal; very little represents true excretion by the

bile or by the mucous membrane of the large intestine. Thus, when sulphaguanidine is injected subcutaneously into cats, only very small amounts appear in the faeces (Hawking, 1942b). When given as a short therapeutic course to man, sulphapyridine, sulphathiazole, sulphadiazine, and sulphanilbenzamide reach the faeces only in small concentrations—e.g., 0–70 mg. per 100 c.cm. (Hawking, 1942a). Uleron apparently reaches the faeces in about the same amount as sulphaguanidine; when 12–18 g. is given during 6 days, about 7 g. appears in the faeces and about 3–4 g. in the urine (Reimers, 1939; Marquardt, 1938). But no report on the use of uleron for bacillary dysentery has appeared.

iii. *Bile*.—Sulphanilamide and other sulphonamides appear in the bile only in concentrations about the same as those in the blood; no large amount of the acetyl derivative appears, so that, although it is formed in the liver, it is not excreted by this route (Hubbard and Anderson, 1940; Spink, Bergh, and Jermsta, 1941; Hubbard and Butsch, 1941). Accordingly sulphonamides are unlikely to have any special influence in cholecystitis beyond their general influence on inflammation anywhere in the body.

iv. *Other Secretions*.—Sulphonamides appear in most of the other excretions and secretions in concentrations similar to those of the blood. Sulphapyridine injected parenterally appears in the gastric juice (apparently by a process of physical diffusion: Davenport, 1942), and this may be the explanation of the vomiting which may occur in such patients. Sulphathiazole appears in the tears in concentrations of 0.1–1.0 mg. per 100 c.cm., but this is not the direct cause of the conjunctivitis which sometimes develops; such conjunctivitis is probably due to acquired sensitivity (Turkell and Wilhelm, 1941).

v. *Milk*.—Sulphonamides appear in the milk of lactating women in amounts similar to those of the plasma. Thus during a therapeutic course the milk may contain sulphanilamide up to 9 mg. per 100 c.cm. (Hepburn, Paxson, and Rogers, 1942), sulphapyridine 3–13 mg. per 100 c.cm. (Föllmer, 1941), or sulphathiazole 0.5–1.5 mg. per 100 c.cm. (Rieben and Druey, 1942), and the infant may receive sulphapyridine 30–40 mg. a day or sulphathiazole about 4 mg. a day. It is the general opinion that the amount appearing in the milk of the mother is too small to exert any effect, toxic or therapeutic, upon the infant.

Blood Concentration

The following Table shows typical blood concentrations after administration of the different sulphonamides:

Compound	Dose	Blood Concentration (mg. per 100 c.cm.)		Reference
		Free	Total	
Sulphanilamide	4 g.	4.0*		
Sulphapyridine	2–4 g. 2–4 g. followed by 1 g. 4- hourly	2.0 (0.5–5.0)* 4.2–6.5	2.6 5.6–8.6	Kinsman, Moore, and Harrison (1940)
Sulphathiazole	1 g. 4-hourly 2 " " 3 " "	4.6 (1.6–8.7) 6.0 (2.2–13.2) 6.5 (3.0–9.6)		Melton (1941)
Sulphadiazine	2 g. 5 g. 4–5 g. 3 g. followed by 1 g. 4- hourly	2.0–3.3* 3.6–5.5* 8.5 (6.7–10.8) (after 24 hrs. 2–4) 9.5 (4.4–19.0)	9.9 (7.9– 12.6) 11.3	Ratish, Shackman, and Bullowa (1942) Peterson, Strauss, et al. (1941) Reinhold, Flippin, et al. (1941)
Sulphamezathine	4 g. followed by 2 g. 6- hourly	6.0 (2.0–13)		Macartney et al. (1942)
Sulphamerazine	3 g. followed by 1 g. 6–8- hourly	10.3 (3.5– 15.0)		Murphy, Clark, and Flippin (1943)
Sulphaguanidine	1–7 g.	1.5–4.0*		Marshall, Bratton, et al. (1940)
Succinyl sulphathiazole	17 g. followed by 3 g. 4- hourly	0.5–1.0 (sul- phathiazole)	1.0–2.0 (succinyl sulpha- thiazole)	Poth and Knotts (1942)

* Blood concentration at about 4 hours after single dose is taken.

Solubilities of Sulphonamide Compounds

The solubilities of the various sulphonamide compounds and their acetyl derivatives are often important. A table of the relevant data is given in M.R.C. War Memorandum No. 10, "The Medical Uses of Sulphonamides," to which reference should be made. Briefly summarized, the compounds may be classified as: (a) relatively highly soluble (>200 mg. per 100 c.cm. at 37° C. and pH 7.4)—sulphanilamide, sulphaguanidine, sulphacetamide, sulphadimethylpyrimidine, and acetyl-sulphanilamide; (b) moderately soluble (50–200 mg. as above)—sulphathiazole, sulphamerazine, acetyl-sulphaguanidine, and acetyl-sulphadimethylpyrimidine; and (c) poorly soluble (<50 mg. as above)—sulphapyridine, sulphadiazine, acetyl-sulphapyridine, acetyl-sulphathiazole, and acetyl-sulphadiazine. The solubility of almost all sulphonamides is greatly increased by making the solution alkaline. The sodium salts of the sulphonamides are extremely soluble, up to one part in three.

Action on Various Organs

Examined by the methods of classical pharmacology, sulphonamides are comparatively inert, and sulphanilamide has no effect upon intestine, uterus, heart, or blood pressure. Given in toxic doses to laboratory animals, it depresses the cerebral cortex and excites subcortical centres, producing coma followed by a condition resembling decerebrate rigidity (Hawking, 1937; Marshall, Cutting, and Emerson, 1938). Similar symptoms of convulsions and rigidity (followed by recovery) have occurred in a 3-year-old child who took 6 g. sulphanilamide (Reed, 1944). A case has also been recorded (Cutts and Bowman, 1941) of a man who was given by mistake 30 g. sodium sulphapyridine during a 10-hour period. The main nervous symptoms were restlessness, vomiting, and hiccup, but no convulsions, twitching, or loss of mental lucidity. When monkeys are given repeated sublethal doses of sulphapyridine or sulphathiazole a characteristic symptom-complex is produced, consisting of anorexia, increasing nausea with or without vomiting, and diarrhoea. The commoner toxic effects which occur in man are too well known to require detailed description. They may be classified as: irritation of alimentary canal (nausea and vomiting); effects on blood cells and bone marrow (haemolytic anaemia, agranulocytosis, thrombocytopenia); effects on blood pigments (cyanosis, methaemoglobinaemia, sulphaemoglobinaemia); sensitization phenomena (drug fever, skin rashes); degeneration of particular organs (jaundice and liver damage, peripheral neuritis); and effects on the brain (mental depression, headache, and dizziness).

Effect on Acid-Base Balance

Sulphanilamide tends to cause a shift in the reaction of the body fluids towards the acid side, bicarbonate being lost from the blood. It has been shown that this effect is primarily due to the renal excretion of more bicarbonate (i.e., the kidney cells reabsorb less bicarbonate from the glomerular filtrate as it flows down the tubules) (McChesney, Sprague, and Marshall, 1941; Höber, 1942); while the hyperpnoea and loss of carbon dioxide from the lungs is a secondary compensation. Accordingly, this effect can be corrected for clinical purposes by giving sodium bicarbonate in doses equal to those of sulphanilamide. There is some evidence that this action of sulphanilamide may possibly be connected with the ability of the drug to inhibit carbonic anhydrase, the enzyme which catalyses the liberation of carbon dioxide from the carbonate of the plasma; as was shown by Mann and Keilin (1940), this enzyme is strongly and reversibly inhibited by sulphanilamide, but not by sulphonamides in which substitutions have been inserted on the $-\text{SO}_2\text{NH}_2$ group; e.g., sulphathiazole. A blood concentration of 3–4 mg. sulphanilamide per 100 c.cm. does not affect the excretion of carbon dioxide from the lungs in men at rest; but in exhausting exercise there is some hindrance, and men taking 2–3 g. sulphanilamide daily are handicapped mentally and physically when required to perform exacting or strenuous work (Roughton, Dill, Darling, Graybiel, Knehr, and Talbott, 1941). On the other hand, men taking 2–4 g. sulphathiazole or sulphadiazine are not handicapped in this way (Roughton, Darling, Forbes, Horvath, Robinson, and Talbott, 1942).

Other Actions

Sulphapyridine has some antipyretic action, which may partly account for the rapid fall of temperature which it causes in patients with pneumonia (Nicolai, 1941). The action of sulphonamides on isolated tissue cells, and their behaviour when applied locally to wounds, have been reviewed by Hawking (1943). Briefly, saturated solutions of the more soluble sulphonamides—e.g., sulphanilamide—have an injurious effect upon cells in tissue culture, but concentrations of less than 50 mg. per 100 c.cm. are usually harmless. When applied to wounds, sulphonamides probably cause slight harm to the tissues, but this is quite trivial compared with that caused by the unchecked growth of bacteria.

When rats are placed on purified diets containing sulphaguanidine or succinyl sulphathiazole (which suppress the growth of the coliform bacilli of the large intestine) growth is diminished and various pathological lesions are caused—e.g., aplasia of the bone marrow, hyaline sclerosis of blood vessels and viscera, dermatitis, and hypertrophy of the thyroid gland. It is considered that these effects are probably due to lack of substances, such as folic acid, which are synthesized by the bacteria of the large bowel (Ashburn, Daft, Endicott, and Sebrell, 1942; Black, Overman, Elvehjem, and Link, 1942; Mackenzie, Mackenzie, and McCollum, 1941).

Notes on the Pharmacology of Some Newer Sulphonamides

Sulphadimethylpyrimidine (sulphamezathine): [2(*p*-aminobenzene-sulphonamido)-4:6-dimethylpyrimidine].

Synthesized by Sprague, Kissinger, and Lincoln (1941), and by others, and introduced (as sulphamethazine) for clinical use by Macartney *et al.* (1942). More soluble than sulphadiazine or sulphamerazine. Rapidly absorbed from the intestine, but slowly excreted, so that a high blood concentration can be produced by moderate dosage. When 4 g. is given by mouth for pneumonia, followed by 2 g. every 6 hours (or 1 g. every 4 hours), the blood concentration of free sulphonamide reaches 8 mg. per 100 c.cm. in 1-3 hours and the subsequent blood level ranges from 2 to 13 (average 6) mg. per 100 c.cm. The total recovery in the urine is usually about 50% of the amount ingested. Judged according to equal blood concentrations, the toxicity and therapeutic potency are similar to those of sulphadiazine. Although both sulphadimethylpyrimidine and its acetyl derivative are comparatively soluble, one case of haematuria and one of urinary suppression occurred in a series of 77 patients (Peters and Easby, 1943). However, renal symptoms are usually rare with this compound.

Sulphamerazine: [2(*p*-aminobenzene-sulphonamido)-4-methylpyrimidine].

Sulphamerazine has recently been described at length in this *Journal* (Feb. 3, 1945, p. 155), so that repetition here is unnecessary. In brief, sulphamerazine is intermediate in solubility between sulphadiazine and sulphadimethylpyrimidine; its activity and toxicity, measured in terms of blood concentration, are similar to those of these two compounds; it is rapidly absorbed and produces a more persistent high concentration in the blood than either of them, so that an adequate level may be maintained by lower and less frequent dosage than is necessary in their case.

Sulphapyrazine: [2(*p*-aminobenzene-sulphonamido)-pyrazine].

Small doses of this compound lead to a relatively high blood concentration, while large doses cause no corresponding increase. Consequently, at a low dose level sulphapyrazine is more active than other sulphonamides, but at a high dose level this advantage disappears. Absorption is somewhat irregular, making its therapeutic effect uncertain; this irregularity would be a handicap for clinical use. As absorption in the intestine is incomplete, large proportions of the ingested dose reach the faeces, and this compound would therefore seem to be suitable for the treatment of bacillary dysentery; but no clinical reports have yet appeared about its use for this condition (Rueggesser, Hamburger, Turk, Spies, and Blankenhorn, 1941; Schmidt and Sesler, 1943; White, 1942).

Sulphaguanidine: [*p*-aminobenzene-sulphonyl-guanidine].

Sulphaguanidine is poorly absorbed when given by mouth, and a considerable portion appears in the faeces, this being the reason which led to its use in the treatment of bacillary dysentery. After doses of 1-7 g. per 70 kg. man, the blood concentration (free) is about 1.5-4 mg. per 100 c.cm., the peak occurring after approximately 4 hours; about 25-30% of the compound in the blood is acetylated. The proportion excreted in the urine after a single dose of 1-7 g. is 10-60%, of which two-thirds are free and one-third is acetylated (Marshall, Bratton, *et al.*, 1940). After a course of 9 g. during 24 hours to a patient, 1.3 g. was recovered from the faeces and 3.1 g. from the urine in 48 hours (Hawking, 1942a). Penetration into the cerebrospinal fluid is low. In dehydrated patients with dysentery in the British Army in Egypt, sulphaguanidine has occasionally caused blockage of the urinary passages. (See also Hawking, 1942b.)

Succinyl sulphathiazole (sulphasuxidine): [2-(*p*-succinyl-amino-benzene-sulphonamido)-thiazole].

This compound, which was introduced by Poth and Knotts (1941), is broken down in the intestine, liberating small amounts of sulphathiazole; the growth of the coliform bacilli (but not that of the streptococci) in the large intestine is thereby suppressed and the faeces become semi-fluid and odourless; about 2-4 motions are passed daily. The compound is recommended for dysentery and for the preparation of patients before undergoing operations on the large intestine. The standard dosage in man is 0.25 g. per kg. initially and 0.04 g. per kg. 6 times daily for maintenance. The urine contains about 5% of the total dose administered. The blood contains about 0.5-1.0 mg. free sulphathiazole per 100 c.cm. and 1.0-2.0 mg. total (i.e., acetyl-sulphathiazole plus succinyl sulphathiazole) (Poth and Knotts, 1942; Poth, 1942).

Phthalyl sulphathiazole (sulphathalidine): [2-(*p*-phthalyl-amino-benzene-sulphonamido)-thiazole].

Introduced by Poth and Ross (1943, 1944) and Kirchhof, Racely, Thompson, and David (1943). It closely resembles succinyl sulphathiazole, but is 2-4 times more active in suppressing the growth of coliform bacilli in the intestine, and it renders the faeces less fluid.

Promanide (U.S.A.: promin): [Sodium salt of *p*-*p'*-diaminodiphenyl-sulphone-N,N'-di(dextrose sulphonate)].

Introduced by Feldman, Hinshaw, and Moses (1940) for the treatment of tuberculosis. It restrains the development of experimental tuberculosis in guinea-pigs, although it does not save all the animals. In human pulmonary tuberculosis it appears to exert a definite slight beneficial effect, but this is balanced by the production of toxic symptoms. It has now been given to several hundred patients. The daily dose is about 1.6 g. (up to 3.2 g.), and this has been continued as long as 6 months. The average blood concentration on this dose is about 2.4 mg. per 100 c.cm. Promanide enters the cerebrospinal fluid only in low concentration. The chief toxic symptoms are diminution of haemoglobin and of erythrocytes in the blood (apparently due to haemolysis), cyanosis, and gastro-intestinal disturbances; rashes, headache, agranulocytosis, and other symptoms have also been reported. It is excreted in the urine (average concentration about 100 mg. per 100 c.cm.), but being soluble it does not cause urinary blockage. The various toxic effects indicate that it should be given only under careful supervision (Hinshaw, Pfuetze, and Feldman, 1943; Heaf, Hurford, Eiser, and Franklin, 1943).

Another compound of this type has been introduced recently—viz., *promizole*.

This is similar in its properties to promanide, but is probably more active and less toxic.

Marfanil (mesudin, homosulphanilamide, sulphamylon): [*p*-amino-methyl-benzene-sulphonamide].

Introduced by I. G. Farbenindustrie, tested biologically by Domagk, and described by Klarer (1941). It had also been prepared independently by Miller, Sprague, Kissinger, and McBurney (1940). It differs from all the other sulphonamides in that the amino group (H_2N) is separated from the benzene ring by a methyl ($-\text{CH}_2-$) group. Accordingly it is not diazotizable and cannot be estimated by Marshall's method. Also, it is not inhibited by *p*-aminobenzoic acid. Marfanil-fast strains of bacteria are not resistant to sulphathiazole, and conversely (Link, 1943). Apparently the receptor of the organism on which it acts is different from that which is susceptible to the usual sulphonamide action. It is more soluble in water than sulphanilamide (1,970 mg. per 100 c.cm. at 37°C .), and very soluble in dilute acids or alkalis. It is less active than sulphanilamide against streptococci. Domagk (1942) claims that it is much more active against anaerobic infections than this compound; but this claim is not confirmed by Schreus, Brauns, and Schümmer (1941). It seems to be used extensively in the German army for local application to wounds as marfanil-prontosil powder (i.e., 1 part marfanil, 9 parts sulphanilamide), and since it is not inhibited by *p*-aminobenzoic acid it may have real advantages for this purpose. Mitchell, Rees, and Robinson (1944) have recently described a clinical trial for use as a local application to infected wounds; they consider it valuable for this purpose. Their trial was made with German material captured at El Alamein (see also *Lancet*, 1944, 1, 635).

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INVESTIGATION AND RESULTS OF TREATMENT OF 1,000 CASES OF VAGINAL DISCHARGE

BY

OSWALD LLOYD, M.D., F.R.C.S., M.R.C.O.G.

Assistant Gynaecological Surgeon, Addenbrooke's Hospital,
Cambridge; Late Gynaecological Registrar,
Middlesex Hospital

The following account embodies the results of the investigation and treatment of 1,000 women complaining primarily of vaginal discharge. Each was carefully interrogated and all necessary bacteriological and serological investigations were made. Details of clinical examination and findings are purposely omitted, as the routine is now well established. The cases were all directly under my care for a period of at least six months. The services of a trained nurse were at all times available, and this has contributed greatly to the excellence of the end-results. The case incidence of the various types will be found in the Table, and each group will be briefly discussed and conclusions drawn from the results.

Case Incidence

(a) Trichomonas vaginitis	447
(b) Gonococcal infection	178
(c) Combined trichomonas vaginitis and gonococcal infection ..	32
(d) Residual and non-specific erosions	193
(e) Monilia vaginitis	57
(f) Vulvovaginitis of infancy	14
(g) Senile vaginitis	41
(h) Non-inflammatory leucorrhoea	27
(i) Polypi, neoplasms, and foreign bodies	11
Total	1,000

(a) Trichomonas Vaginitis

The literature dealing with this condition is considerable. At first there seemed to be some doubt as to the pathogenicity of the organism, but now it is widely accepted as capable of producing a vaginitis—acute, subacute, and chronic. The primary source of the infection is still debated: the rectum is a potential origin, but is by no means definitely incriminated. Almost all cases occur during the reproductive period, but this series includes one pre-pubertal and four post-menopausal. It affects undoubted virgins and has a predilection for the vagina in pregnancy. The association of gonorrhoea and trichomonas vaginitis in 32 cases draws attention to the need for careful exclusion of Neisserian infection even if *Trichomonas vaginalis* has been demonstrated. The following method of treatment has yielded the best results, both immediate and remote.