SURGICAL PROCEDURES IN GENERAL PRACTICE

This is one of a series of articles contributed by invitation

SULPHONAMIDE CHEMOTHERAPY IN SURGICAL INFECTIONS—I

BY

A. J. COKKINIS, M.B., B.S., F.R.C.S.

Sulphonamide chemotherapy is not a "surgical procedure," but is now being applied to surgical infections. So much has been written upon the subject of the "new chemotherapy" and it is still so "new" that it is impossible to dogmatize about it. It is possible, however, to present briefly the impressions gained from my own experience of some fifteen hundred cases.

Successful application of the new treatment is not easy, and haphazard administration on the "hit or miss principle" is worse than useless. Indeed the more one sees of it the more one is led to regard it as a double-edged weapon, capable of doing great good, but also of inflicting serious damage, not all of which is attributable to the toxic properties of these compounds. These drugs cannot of themselves "cure" any bacterial infection. Their sole action is, under favourable circumstances, to produce a condition of bacteriostasis (arrest of bacterial growth) that lasts no longer than the period during which they are administered. The ultimate result of an infection, therefore, still depends on the immunity reaction of the patient, and unless this can dispose of the organisms temporarily arrested by the chemotherapy either the treatment will prove a failure or a relapse of the infection will occur when it is discontinued. Furthermore, by their very ability to arrest bacterial growth these compounds, if given before immunity has had time to develop, may actually inhibit the anti-bacterial response of the body, thus leaving the patient with a "latent" infection but without the means to combat it or to deal with the "flare-up" which may occur when the treatment is stopped. In my belief this potential and as yet largely unrecognized danger of the new chemotherapy far outweighs the risk of damage by the toxic properties of the drugs. If this danger is to be avoided, and if optimum effects are to be obtained from the chemotherapy, the latter must be "timed" so as to coincide with the development of a fair degree of immunity. Moreover, it has been repeatedly shown that far better end-results are obtained from chemotherapy combined with immunotherapy (for example, vaccines) than from chemotherapy alone.

Selectivity of Action

The anti-bacterial action of sulphonamide compounds is highly selective. Only certain bacteria are susceptible, and it is therefore irrational to treat an infection with such compounds unless it is known in advance that one of these bacteria is responsible. Even susceptible bacteria respond differently to the treatment: some can be inhibited by small doses over a short period, others require larger dosage and a longer administration. Moreover, the response of any one organism is inconstant, some strains being more susceptible than others, and even the susceptibility of an individual strain in the same patient sometimes seems to vary from time to time. Other factors apart from variations in immunity and bacterial sensitivity influence the response to sulphonamide chemotherapy. Thus to obtain optimum results it is necessary to maintain

the concentration of these compounds in the body at an effectively bacteriostatic level throughout their administration. The more potent of these compounds are very diffusible, and are excreted almost as rapidly as they are absorbed. To maintain an effective concentration they must therefore be given in adequate doses, properly "spaced," and the administration must be uninterrupted. Inadequate dosage and too short a period not only fail to do any good but seem to lead to the development of acquired resistance on the part of the organism to the drug ("sulphonamide-fastness"), which may produce complete non-response to subsequent chemotherapy, however intensive this may be.

To attack a bacterial focus the sulphonamide must be brought to it by the blood stream: an adequate blood supply to an infected area is therefore essential to success. I have seen many failures of chemotherapy attributable to the presence of avascular foci, such as infected blood-clot (for example, in thrombosed veins and cardiac vegetations), patches of necrotic tissue, abscesses embedded in fibrous tissue or sclerosed bone, and infected areas with local vascular failure following venous stagnation, thrombosis, or pressure by an inflammatory exudate. In some of these cases success was ultimately obtained by improving the blood supply of the focus with such measures as physiotherapy or surgical relief of tension. Finally, no chemotherapeutic agent can deal with an infection from an unlimited source of bacterial contamination, however sensitive the bacteria may be. Thus, it is futile to treat a general peritonitis with sulphonamide when there is a source of continuous infection, such as a perforated appendix or strangulated loop of intestine, unless this has been previously removed.

The number of bacteria now known to be sensitive to sulphonamide compounds already includes the following: haemolytic streptococci, certain non-haemolytic streptococci (for example, *Strep. viridans* and *Strep. faecalis*), *B. coli* and other members of the coliform group, certain pneumococci, the gonococcus, the meningococcus, and probably certain anaerobes, such as *Cl. welchii*.

Sulphonamide Compounds and their Nomenclature

Thus far I have made a trial of eight sulphonamide-containing substances. Although these do not constitute all the sulphonamide compounds manufactured to date, they are the best known and most thoroughly investigated of them. Much uncertainty exists in the minds of practitioners as to the nature of these compounds, partly on account of their complicated chemical structure but also because of the confusing and unnecessarily involved nomenclature adopted by manufacturers. The essential chemistry of these compounds is not difficult to understand. They all contain at least one benzene group (C_6H_5 , shown usually in the form of the benzene ring $\langle \bigcirc \rangle$), at least one amino group (NH_2), and at least one sulphonamide group (NH_2SO_2). If we start with benzene and add an amino (NH_2) group to it we obtain aminobenzene ($\langle \bigcirc \rangle \text{NH}_2$), which is the chemical name for aniline. By attaching a sulphonamide group (NH_2SO_2) to the side (para) of aminobenzene, we obtain para-aminobenzenesulphonamide ($\text{NH}_2\text{SO}_2 \langle \bigcirc \rangle \text{NH}_2$). A shorter name for this is obviously aniline sulphonamide, which has been further abbreviated

to "sulphanilamide"—and so we arrive at the simplest and best known of all sulphonamide compounds. The other compounds are either modifications of sulphanilamide or substances with a more complicated chemical structure, but they all contain the above three groups.

Sulphanilamide (para-aminobenzenesulphonamide).—This is the compound which until quite recently has shown the greatest bacteriostatic potency and the widest anti-bacterial range. It is mostly manufactured in the form of oral tablets ($7\frac{1}{2}$ grains or 0.5 gramme), but unfortunately under so many different trade names that much confusion has arisen over its nomenclature. "Sulphanilamide" and "para-aminobenzenesulphonamide" are the only chemically correct names for it, but it is sold by various British and foreign firms under the following synonyms: sulphonamide-P, streptocide, prontosil album, colsulanyde, P.A.B.S., and prontylin. All these names refer to the same drug—sulphanilamide. An extremely diffusible substance, it is rapidly excreted in the urine, in which it can be estimated by a simple quantitative test. Sulphanilamide arrests the growth of all sulphonamide-susceptible organisms with the exception of the pneumococcus, but it is apt to cause certain toxic effects. Its effective dosage and period of administration vary with the causative organism, the weight of the patient, the site and nature of the infection, and the degree of immunity. Sulphanilamide has the advantage of being very considerably cheaper than most of the other sulphonamide compounds.

T 693.—Recently a compound of sulphanilamide and pyridine (para-aminobenzenesulphonamido-pyridine) has been introduced by Messrs. May and Baker (at present known as T 693), which shows a bacteriostatic potency at least equal to that of sulphanilamide and a wider anti-bacterial range, since it acts on pneumococci as well as on the other susceptible organisms. Unfortunately, in my hands it has proved even more toxic than sulphanilamide.

The Prontosil Drugs.—Prontosil rubrum (oral tablets) and prontosil soluble (by injection) are the original compounds (Bayer) with which the new chemotherapy started. They are highly complicated chemical substances, their full names being diamino-azo-benzol-sulphonamide (prontosil rubrum) and disodium-acetylaminooxynaphthalenedisulphonate (prontosil soluble). Although their action is similar to that of sulphanilamide (into which they are partly converted in the body), their anti-bacterial range and potency are less extensive. But they have the advantage of being less toxic, and I have found prontosil soluble (in doses of 10 to 30 c.cm. of the 5 per cent. solution daily) particularly useful in major operation cases.

Proseptasine and Soluseptasine.—These drugs (May and Baker) are the least toxic of all the sulphonamide compounds. Unfortunately they also appear to be the least potent and to have the narrowest anti-bacterial range. Proseptasine (oral tablets) is a benzyl derivative of sulphanilamide (para-benzylaminobenzenesulphonamide), while soluseptasine (for injection) has a very complicated structure (disodium-phenylpropylaminobenzenesulphonamido-disulphonate) in some respects similar to that of prontosil soluble.

Uleron.—This compound (Bayer) is given in the form of oral tablets, and is much thought of in Germany; it differs from all the above in having two sulphonamide groups (disulphonamide). I have used it in some 200 cases of gonococcal, streptococcal, and coliform infections, and have found it relatively free from immediate toxic effects. Its anti-bacterial action, however, has proved very capricious, and one cannot help thinking that this may

in part be due to its low solubility in neutral media, and probably, therefore, to its relatively poor diffusibility. Striking clinical improvements have followed its administration, but a rather low proportion of bacteriological cures.

Rubiazol.—At present I am making a trial of this compound (carboxy-sulphonamido-chrysoidine), made by Messrs. Roussel and extensively used in France. It appears to be relatively non-toxic, but I am not yet able to speak authoritatively of its anti-bacterial range or effectiveness.

Toxic Effects of the Compounds

On the whole it seems that the more effective a sulphonamide compound is against bacteria the more toxic it is to man. Thus, sulphanilamide and T 693, the two compounds which have shown the highest potency and widest anti-bacterial range, have also produced the highest incidence of toxic by-effects. These toxic effects may be divided into three groups, according to their severity and importance:

(a) *Mild*—of no significance, and not indicating cessation of the chemotherapy.—These are extremely common, and include headache, giddiness, muscular weakness, loss of energy, and other nervous symptoms; nausea, anorexia, and constipation; slight cyanosis, chilliness, palpitations, slight dyspnoea, and mild urticarial rashes. Fortunately, most of these symptoms tend to pass off after the first few days, owing to the development of tolerance to the drugs. Also, they can be mitigated to some extent by rest and fresh air, by cutting down the ingestion of sulphur, and by giving glucose and free fluids.

(b) *Moderate*—of no serious significance, but usually demanding cessation of the chemotherapy.—These occur in about 10 per cent. of patients taking sulphanilamide, and include vomiting, diarrhoea, prostration, mental changes, fever, extensive skin rashes (morbilliform and scarlatiniform), oedema, and marked cyanosis, pallor, or dyspnoea. The last three symptoms always indicate a complete examination of the blood.

(c) *Serious*—demanding immediate cessation of chemotherapy, repeated blood examinations, and appropriate therapeutic measures, which should include an attempt to get rid of any sulphonamide in the intestine by colonic wash-outs. The serious effects are: (i) destructive blood changes—for example, agranulocytosis and haemolytic anaemia; (ii) extensive purpuric rashes with high fever; (iii) toxic jaundice; (iv) toxic nephritis. In 1,500 cases I have seen only six examples of these serious effects, all of them recovering completely. I have yet to experience a case of agranulocytosis or other serious blood damage.

The other sulphonamide compounds have produced very little in the way of immediate toxic effects, but one of them—uleron—has the unique property of occasionally causing a peripheral neuritis. This does not occur unless the drug is given continuously over a period of more than seven days.

Gingivitis and Pyorrhoea

This disease is primarily a streptococcal gingivitis, and although there are many predisposing causes the teeth themselves may be quite sound. It starts with redness, swelling, and tenderness of the gums, which become spongy and bleed easily. The disease may be partly arrested at this stage, or it may pass on to suppuration and a genuine pyorrhoea. The infection of the gum becomes associated with a rarefying osteitis of the alveolus, leading to absorption of bone, and so to exposure, loosening, and finally casting off of the teeth. Conservative treatment, thus far, has been very unsatisfactory, as is shown

by the frequent use of such radical procedures as wholesale dental extraction and gingivectomy.

Some eight months ago, through the courtesy of Professor A. Fleming, a number of cases were investigated at St. Mary's Hospital in a research undertaken with Dr. C. W. Morley. It was found that the outstanding organisms were *viridans* streptococci, while haemolytic streptococci and other bacteria were less often discovered. We then started to treat cases with sulphonamide compounds, under full bacteriological control. We have succeeded, after many disappointments, in evolving a technique which yields a high proportion of excellent results, both clinically and bacteriologically, provided the cases are treated before there is loosening of the teeth or serious retraction of the gums.

Smears and cultures are taken at the start of treatment, and weekly afterwards. For the first two or three weeks the patient is given injections (twice weekly) of a parodontal streptococcal vaccine, which are continued for a minimum of six weeks. Sulphonamide chemotherapy is started in the third or fourth week. Relapses are very common after only one course, and it was found that at least three 14 to 21 day courses had to be given (with intervals of two to four weeks) to obtain lasting improvement. Most of the cases have been given sulphanilamide (2 to 4 grammes daily), but we are now using T 693 with equally promising results. No local treatment is employed.

Ulcerative Stomatitis and Pharyngitis

During the work mentioned a number of cases were seen of chronic and relapsing septic ulcers of the mouth, palate, and pharynx, from which *viridans* or haemolytic streptococci were obtained on culture. They all responded to sulphonamide therapy clinically and bacteriologically in a matter of days, but most of them relapsed afterwards. We are now treating them along the same lines as the gingivitis cases—that is, with multiple courses of sulphanilamide and vaccine—and the good results appear to be much more lasting. Quite recently I obtained complete resolution in two days of a large acute streptococcal ulcer of the fauces with severe oedema. Sulphonamide chemotherapy would also seem to be worth trying in cancrum oris.

Acute Tonsillitis

My experience with sulphonamides in this condition is limited to cases of follicular (streptococcal) tonsillitis, Vincent's angina, and quinsy. The Vincent's angina cases failed to respond, but the follicular and suppurative tonsillitis resolved in twenty-four to forty-eight hours, although the actual follicles in follicular cases persisted for several days. Three of the follicular tonsillitis cases relapsed after only two days' treatment, and I now continue the chemotherapy for at least five days. All that the treatment seems to do in these acute cases is to hasten recovery, but one is perhaps justified in hoping that it may also prevent such complications as a septic adenitis or rheumatism. Quite moderate dosage of sulphanilamide (1.5 to 3 grammes daily) appears sufficient to overcome the infection, while the less toxic sulphonamides (for example, uleron or proseptasine) produce an equally striking, if a trifle slower, clinical improvement.

Sinusitis

Thus far I have treated three cases of chronic maxillary sinusitis and one of ethmoiditis with sulphonamides. Two of the maxillary cases were bilateral, of many years'

standing, and had had several operations. Streptococci were obtained on culture, and both patients were ultimately made well, although one required no fewer than five courses of sulphanilamide and the other three courses. The third maxillary case, also very chronic, gave a growth of pneumococci as well as streptococci, and was treated with T 693 after preliminary vaccine. He improved rapidly, but was very intolerant to the drug; subsequently he was given two courses of sulphanilamide, and is now quite free from symptoms. The case of ethmoiditis (streptococcal) showed no response to a longish course of sulphanilamide, but there was extensive necrosis of the skull before the chemotherapy was begun.

The first three cases suggest that chemotherapy can influence even the chronic relapsing type of sinusitis. I do not know how long these patients will remain well, but I believe that repeated chemotherapy combined with vaccine will at least make relapses less frequent. As yet there has been no opportunity of treating primary acute sinusitis, but one has every reason to believe that it would respond more easily and more permanently than the chronic variety.

Otitis and Mastoiditis

Sulphonamide chemotherapy has already established itself as a valuable adjunct in the surgical treatment of these conditions; it has also proved of life-saving value in the streptococcal meningitis which may occur as a complication. But it cannot be stated too strongly that no anti-bacterial remedy should be used as an alternative to operative drainage of a suppurating focus in regions as dangerous as the tympanum and mastoid.

(To be continued)

THE PHYSICAL BASIS OF ALCOHOLIC MENTAL DISORDERS

LECTURE BY PROFESSOR MAPOTHER

The seventeenth Norman Kerr Memorial Lecture was delivered at Friends House, Euston Road, on October 11 by Professor EDWARD MAPOTHER, professor of psychiatry, University of London. The chair was taken by Mr. Arthur Evans, F.R.C.S., president of the Society for the Study of Inebriety, under whose auspices the lecture is instituted.

Professor Mapother, discussing first of all the questionable results of alcohol, said that some findings appeared to support the conclusion that the expectation of life among insured persons was greater for abstainers than for even moderate drinkers. But it was uncertain how far this might be due to the fact that the so-called moderate was in reality immoderate at the time of insurance or became so subsequently. On the other hand, many of the most cherished beliefs of popular medicine as to the value of alcohol had gone, such as that, for instance, it kept out the cold, or formed a suitable ingredient of cooling drinks in summer. There seemed to be no foundation for the belief that it was indispensable to avert tropical infections or to ward off chill. The least justifiable of all kinds of drinking was drinking "by doctor's orders."

On the possible value of alcohol as a food, Sir Frederick Gowland Hopkins, as reported in the *British Medical Journal* of December 11, 1937 (p. 1184), had pointed out that experiment did not indicate that muscular exercise increased the rate of combustion of alcohol, which was the real issue. While alcohol was certainly destroyed