Editorials

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Sulphasalazine in rheumatoid arthritis: an old drug revived[1]

Sulphasalazine (SAS) is an old drug. It was synthesized over 40 years ago by Nanna Svartz and her co-workers, Askelof and Willsteadt (Svartz 1942). The drug is a compound of sulphapyridine and 5-aminosalicylic acid (5-ASA) linked by an azo bond. Unlike many other drugs, sulphasalazine was not a chance find, but was deliberately synthesized in an attempt to combine the therapeutic properties of salicylates and sulphonamides with the aim of creating an effective treatment for rheumatoid arthritis (RA). The choice of salicylate as one component is not surprising. The benefits of salicylates in RA are obvious though, as Svartz herself notes, 'the salicylic preparations ... have an excellent effect on the sensations of pain, but have little effect, especially in chronic cases, on the state of the disease otherwise'.

The choice of a sulphonamide as the other component is perhaps more surprising. However, in 1938, when Svartz started her work on SAS and related compounds, RA was widely believed to be an infection of the joints and therefore potentially responsive to antibiotics. The only antibiotics then available were sulphonamides. Certain of these, such as sulphaguanidine, had been tried without success. Svartz reasoned that if the site of the lesion in RA was in connective tissue, a sulphonamide with an affinity for connective tissue ought to be more successful than others. The demonstration by her colleague Helander of this affinity for connective tissue amongst all the azo compounds which they had synthesized, particularly SAS, led Svartz to concentrate research on this drug. Between 1940 and 1946, Svartz treated over 400 cases of RA with SAS and reported a favourable result in 63% (Svartz 1948). Using this experience, she recommended a starting dose of 6 g daily and that this be reduced to 1.5 g daily as soon as the patient improved. She emphasized that 'treatment for a brief period, e.g. one month, is useless in chronic polyarthritis', but found that SAS therapy was often disturbed by the occurrence of toxic manifestations. In cases where patients developed high fever and rash shortly after starting SAS, she recommended stopping the high dose of SAS and re-starting at a very low dose (1/8–1/4 g, 2–3 times daily initially). The dose could then gradually be increased over the next 10 to 14 days. Unfortunately, when Sinclair & Duthie (1948) attempted to repeat Svartz's original work, they failed to follow these guidelines. They carried out an open study on 60 patients with active rheumatoid arthritis: all were treated with hospital admission, bed rest and physiotherapy. Twenty were in addition given gold injections and 20 SAS. All 60 patients initially improved, but after discharge all three groups deteriorated and at final follow up there were no significant differences between the controls (i.e. bed rest and physiotherapy alone) and patients treated with gold or SAS.

However, as the authors themselves pointed out, 'the total dose and length of course [of SAS] were not those recommended'. Treatment with SAS was given for a mean duration of only 60 days, and at final follow up a mean of 6.5 months after the start of the trial only one of the original 20 patients was still taking SAS. The same problem applied to the gold-treated group. These patients were treated with gold for a maximum of 15 weeks, but assessed after eight months. This hiatus probably accounts for the relapses in this treatment group; it was subsequently shown by Rothermilch *et al.* (1976), and is now generally accepted, that gold therapy must be maintained if relapses are to be prevented.

The reason given by Sinclair & Duthie (1948) for their short courses of SAS was a high incidence of adverse effects, particularly nausea. Svartz had already encountered this problem, albeit infrequently. Since the tablets were identical (Svartz supplied Sinclair & Duthie), the difference may have been racial. Svartz's patients were Swedish and Sinclair and Duthie's British. In this context it is notable that the British appear more susceptible to aspirin-induced dyspepsia than, for example, North Americans (Bird & Wright 1982).

Sinclair and Duthie's management of dyspepsia and other adverse effects was to stop SAS and reintroduce it at a full dose of 6 g daily after a short break. Our own experience suggests that they may have had more success if SAS had been reintroduced at a low dose and then gradually increased. Sinclair and Duthie's comment on the short course used was, 'with regard to the length of the course, it is generally admitted that if any single method of therapy is continued for long enough in RA, it is likely that a natural remission

of the disease will occur, and credit may be wrongly given to that particular remedy'. However, their own finding that nearly half the original 60 patients had relapsed at final follow up casts doubt on this statement.

Svartz meanwhile turned her attention to ulcerative colitis, where she had also found SAS beneficial. Her findings were soon supported by others (Misiewicz *et al.* 1965), and the use of SAS in RA was abandoned in favour of newer therapies such as gold and steroids.

Interest in the use of SAS in RA was reawakened some 20 years later by McConkey and colleagues in Birmingham. He had previously studied the use of dapsone in rheumatoid arthritis and found it to be effective (McConkey *et al.* 1976). Following this, he decided to investigate drugs which shared some of dapsone's properties, one of which was SAS. Dapsone is a sulphone and is therefore related to sulphonamides. Sulphapyridine, like dapsone, has been used in dermatitis herpetiformis, where deposition of immune complexes is thought to play a major pathogenetic role. Thus, the possible immunomodulating role of sulphapyridine in other conditions led to McConkey's renewed interest in SAS. He was at first unaware of Svartz's and Helander's work.

Initially 32 patients with active RA were given SAS in an open study (McConkey *et al.* 1978). Twenty-five continued the drug for at least a month, and the majority showed substantial symptomatic improvement as well as falls in the ESR and serum C-reactive protein concentrations. The remaining patients developed adverse effects, mainly nausea and headaches, though two developed megaloblastic anaemia (one due to vitamin B_{12} deficiency and one to folate deficiency). In addition, one patient developed neutropenia which resolved rapidly on withdrawing SAS.

The overall impression from this study was of an effective drug with a high frequency of side effects, particularly nausea and headaches. In this small study, neutropenia was a worrying feature. However, a survey of the literature at the time revealed that in the ten-year period between 1964 and 1973, during which 124 000 prescriptions for SAS were issued, only 8 cases of neutropenia had occurred, with one death (Committee on Safety of Medicines 1977).

McConkey *et al.* (1980) extended their work on SAS in RA with an open study in 74 patients receiving a maintenance dose of 2 g enteric-coated SAS daily. Eighteen patients failed to respond, 7 stopped treatment because of adverse effects, and the remainder improved.

Bird *et al.* (1982) proceeded to study SAS using the 'patient-model system'. This system, developed in Leeds over the preceding years, had already been used to compare the efficacy of sodium aurothiomalate, D-penicillamine, hydroxychloroquine, aspirin and alclofenac in RA. Fifteen patients fulfilling stringent criteria for active rheumatoid arthritis are first observed for a short period whilst receiving a non-steroid anti-inflammatory drug alone, then prescribed the test drug and monitored using a large number of clinical and laboratory variables for six months. In this 'patient-model system' gold, penicillamine and hydroxychloroquine had been found to be effective. Aspirin and alclofenac were ineffective and SAS produced results comparable with, though perhaps not quite as good as, penicillamine and gold.

The natural progression from these open studies was to a controlled, blinded trial. A two-centre study was set up to compare the efficacy of SAS with a drug of established value in RA, D-penicillamine, at the Rheumatism Research Unit, Leeds and Dudley Road Hospital, Birmingham (Neumann *et al.* 1983). Sixty-three outpatients with active RA were studied, 32 in Birmingham and 31 in Leeds. After a four-week period taking a non-steroid anti-inflammatory drug alone, 31 patients were randomly allocated to SAS treatment and 32 to D-penicillamine. SAS was increased slowly from an initial dose of 0.5 g daily to a maintenance dose of 2 g daily. Initially 125 mg D-penicillamine was administered daily; this was increased gradually to a 500 mg daily maintenance dose. Both groups were monitored using a number of clinical tests (global clinical score, morning stiffness, grip strength, articular index, pain score), and the ESR and serum C-reactive protein were also recorded.

By the end of the study all clinical and laboratory tests of disease activity, with the exception of grip strength in those receiving D-penicillamine, had shown substantial and significant improvements. The improvement appeared slightly earlier in the SAS-treated group, possibly reflecting the policy of increasing SAS to full dosage over four weeks, whereas with D-penicillamine full dosage (500 mg daily) was only achieved after eight weeks. In this study, failure to respond to treatment was uncommon. Only 2 patients in the SAS group and 4 in the D-penicillamine group were withdrawn for this reason. However, adverse effects necessitating stopping treatment were frequent in both groups: 8 patients taking SAS and 12 patients taking D-penicillamine were withdrawn from the study. This raises some problems in interpretation of results. In an attempt to minimize this, all

patients who withdrew from the study for whatever reason were excluded from analysis and the remaining patients analysed using paired non-parametric statistical tests. Nevertheless, larger and more prolonged studies of SAS in RA are needed to establish its role as a long-term agent.

Assuming such studies confirm the above results, two questions about SAS will need to be answered: how does it work and what can be done to minimize the adverse effects? Rheumatoid arthritis cannot be explained purely in genetic terms and is undoubtedly triggered by an evironmental antigen. Numerous suggestions for such an antigen have been put forward, one of which is that *Clostridium perfringens* in the bowel may trigger the disease (Olhagen & Mansson 1968). Thus RA may be an enteropathic arthritis (*British Medical Journal* 1979). SAS has previously been demonstrated to alter faecal flora in patients with inflammatory bowel disease (West *et al.* 1974). The drug also possesses immunosuppressive properties (Rubinstein *et al.* 1978). It is one of a small group, notably including gold and penicillamine, which can induce selective IgA deficiency (Delamere *et al.* 1983). In an extension of the controlled trial of SAS versus D-penicillamine in RA described above (Neumann *et al.* 1983), we examined the faecal flora of patients in both treatment groups and in a normal control population (patients attending a fracture clinic) to assess whether any differences could be detected in the faecal flora carried by RA patients compared with normal controls, and to assess whether the faecal flora in the RA patients altered during therapy. Our provisional findings indicated an increase in *Clostridium perfringens* carriage in patients with RA compared with controls, supporting the observation made earlier by Olhagen & Mansson (1968). During therapy there was a trend towards a decrease in *Clostridium perfringens* count in the SAS-treated group which was not seen in the D-penincillamine group. However, our results in the small group of patients studied did not achieve statistical significance, and the work is being extended to further patients with RA (Neumann *et al.*, in preparation). A positive result would be good circumstantial evidence that SAS works via its antibacterial rather than immunosuppressive effects, as well as supporting the concept of RA as an enteropathic arthritis.

At least 50% of SAS is metabolized into its two major components, 5-ASA and sulphapyridine, by bacterial flora in the large bowel. This raises the question of which of the three drugs, the parent compound sulphasalazine or one of its two components, is active in RA. McConkey *et al.* (1978, 1980) suggested that 5-ASA was the

least likely contender for two reasons: the drug is derived from salicylic acid, a substance known to have no 'second-line' action in RA; and 5-ASA is barely absorbed from the gut, unlike SAS and sulphapyridine (Das & Dubin 1976). Against this we should bear in mind that 5-ASA has recently been shown to maintain remission in ulcerative colitis (Dew *et al.* 1982). Furthermore, its structure closely resembles para-aminosalicylic acid, an antibiotic with antituberculous activity. Both of these features should make us wary of dismissing 5-ASA as simply a salicylate. We are currently investigating its efficacy and anti-bacterial spectrum in patients with RA.

There is a large anecdotal literature suggesting that sulphapyridine *per se* is ineffective in RA (Margolis & Eisenstein 1940, Coggeshall & Bauer 1938, Svartz 1942). In one recent attempt to repeat the use of sulphapyridine, severe nausea precluded a prolonged study of the drug (D Swinson, personal communication). In our own department we are currently also attempting RA treatment with sulphapyridine as part of a formal controlled trial: early results, however, have been discouraging (A Taggart *et al.*, in preparation).

The problem of identifying the active component in SAS is closely linked with that of overcoming side effects. Sulphapyridine causes nausea when given alone and is thus likely to be responsible for SAS-related nausea. Other common adverse effects of SAS such as fever, rashes, and the much rarer neutropenia can also be attributed to the sulphapyridine component. Sulphapyridine produces one further important side effect, male infertility, due to a reduced ability of sperm to penetrate ova. This was first observed by Levi *et al.* (1979), has been confirmed by others (Traub *et al.* 1979), and is a problem shared by other sulphonamides such as sulphamethoxazole. All of these factors limit study of sulphapyridine. The results available on the use of 5-ASA in ulcerative colitis indicate that it is better tolerated than sulphasalazine. It would be fortunate if 5-ASA also proved to be both effective and well-tolerated in RA.

SAS is an old drug revived! Its use in ulcerative colitis may be superseded by 5-ASA, but in RA it is just beginning to gain popularity. The preceding paragraphs have concentrated on its adverse effects, but on present experience SAS appears to carry considerably less hazard to the rheumatoid patient than its established alternatives such as gold and penicillamine.

V C Neumann
Rheumatism Research Unit
University of Leeds
K A Grindulis
Dudley Road Hospital, Birmingham

References

Bird H A, Dixon J S, Pickup M E *et al.*
(1982) *Journal of Rheumatology* 9, 36–45
Bird H A & Wright V
(1982) Applied Drug Therapy of the Rheumatic Diseases.
Wright PSG, Bristol; pp 77–78
British Medical Journal
(1979) i, 1104
Coggeshall H C & Bauer W
(1938) *Journal of the American Medical Association* 111,
2042–2043
Committee on Safety of Medicines
(1977) Extracts for the Register of Adverse Reactions. CSM,
London
Das K & Dubin R
(1976) *Clinical Pharmacokinetics* 1, 406–425
Delamere J P, Farr M & Grindulis K A
(1983) *British Medical Journal* 286, 1547–1548
Dew M J, Hughes P, Harries A D, Williams G, Evans B K &
Rhodes J
(1982) *British Medical Journal* 285, 1012
Levi A J, Fisher A M, Hughes L & Hendry W F
(1979) *Lancet* ii, 276–278
Margolis H M & Eisenstein V W
(1940) *Journal of the American Medical Association* 114,
1429–1433
McConkey B, Amos R S, Butler E P, Crockson R A, Crockson
A P & Walsh L

(1978) *Agents and Actions* 8, 438–441
McConkey B, Amos R S, Durham S, Forster P J G, Hubball S &
Walsh L
(1980) *British Medical Journal* 280, 442–444
McConkey B, Davies P, Crockson R A, Crockson A P, Butler M
& Constable T J
(1976) *Rheumatology and Rehabilitation* 15, 230–234
Misiewicz J J, Lennard-Jones J E, Connell A M, Baron J H &
Avery Jones F
(1965) *Lancet* i, 185–188
Neumann V C, Grindulis K A, Hubball S, McConkey B &
Wright V
(1983) *British Medical Journal* 287, 1099–1102
Olhagen B & Mansson I
(1968) *Acta medica Scandinavica* 184, 395–402
Rothermilch N O, Philips V K, Bergen W & Thomas M H
(1976) *Arthritis and Rheumatism* 14, 533–538
Rubinstein A, Das K M, Melamed J & Murphy R A
(1978) *Clinical and Experimental Immunology* 33, 217–224
Sinclair R J G & Duthie J J R
(1948) *Annals of the Rheumatic Diseases* 8, 226–231
Svartz N
(1942) *Acta medica Scandinavica* 110, 577–598
(1948) *Rheumatism* 4, 180–186
Traub A I, Thompson W & Carville J
(1979) *Lancet* ii, 639–640
West B, Lendrum R, Hill M J & Walker G
(1974) *Gut* 15, 960–965

Hormonal aspects of ovarian malignancy

Ovarian cancer is the second most common malignancy of women and caused 3784 deaths in England and Wales in 1978 (Mortality Statistics 1980). Four thousand one hundred and seventy-nine women were registered as having carcinoma of the ovary in 1974 (Cancer Statistics 1980) and the limited success of current conventional therapy is therefore striking, with less than 10% of women surviving more than 4 years. Survival may be poor because of the frequency with which the disease presents in an advanced state, with only 30% of women having localized disease at presentation (Julian & Woodruff 1969). Treatment programmes are mainly directed towards the investigation of the efficacy of combined modality approaches using combination chemotherapy and surgical debulking of the tumour mass. The frequency of this approach contrasts with the relative paucity of investigations into the possible hormonal sensitivity of this tumour. It has led to no significant increase in 5-year survival over the past 20 years (Tobias & Griffiths 1976). As will be demonstrated, current hormonal therapeutic options are more limited than a study of the origins of ovarian cancer would lead one to expect.

Epidemiology
Epidemiological factors point to a hormonal basis for ovarian cancer, and these strikingly parallel those cited for carcinoma of the breast. Breast cancer predisposes to the development of ovarian cancer, increasing the subsequent risk twofold; whilst carcinoma of the ovary increases the chance of breast cancer by 3 to 4 times (Lingeman 1974). The incidence of cancer of the ovary increases with age, apart from a decrease at 50–54 years (Lingeman 1974), and this is a feature of breast cancer in those countries with a high incidence of the disease. Ovarian cancer exhibits a similar racial variation to breast cancer, occurring with greater frequency in Caucasians than Japanese (Haenszel & Kurihara 1967). In both malignancies an environmental factor is suggested by the increased incidence of ovarian and breast cancer in Japanese migrants to Hawaii and California (Buell & Dunn 1965). Carcinoma of the ovary is classically described in nulliparous women and, just as in breast cancer, there is an inverse relationship between parity and the risk of development of ovarian cancer (Newhouse *et al.* 1977). It is not obvious whether an ambience of low fertility predisposes to ovarian cancer, or that women with ovarian cancer are less fertile than matched control groups. Although the association between parity and ovarian cancer suggests that oestrogen deficiency predisposes to