measured using the Barthel index). At that time depression in the carer was associated with the perception, by the carer, that the patient's recovery was poor. This may be simply a pessimistic view secondary to depression or it might indicate that the carer was doing more for the patient than was necessary. As activities of daily living indices have limited sensitivity, and there was also a notable correlation between a patient's perception of his recovery and depression in the carer, depression in the carers of apparently independent patients might have been associated with minor disability in the patient.

One hypothesis that could explain our findings is that depression in the carer was related to the occurrence of a major, life threatening illness and not due to the physical stress of caring. The fact that carers of more disabled patients were initially more upset could simply be because the obviously more severe stroke might engender more worry about the future. As time passed this might lessen. In support of this hypothesis we have shown that increased help for patients at home did not decrease stress on the carer[9] and that almost all disabled patients at home had help from community services (unpublished observations). Moreover, the most commonly expressed mood change was an increase in anxiety, which factor analysis suggested was part of a non-specific alteration in affect.

We must emphasise that this study has investigated only one aspect of the potential stress on carers. It has not directly measured the financial costs, the reduction in the carer's social life, the effects on family or marital relationships, or the effects on the physical health of the carer. These are also important.

We conclude that companions of the survivors of a stroke showed some emotional distress, most commonly anxiety. This was only partly related to the extent of the physical disability engendered by the stroke. Possibly adequate community support was given to patients with physical disability, or possibly many carers adapted well to the patient's disability. By two years depression in the carer was unrelated to any of the patient factors measured, suggesting that other factors influenced the prevalence of depression. For example, increased personal support, such as given by stroke support groups, may be more important than extra physical support in reducing depression in the carers.

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Sulphasalazine for rheumatoid arthritis: toxicity in 774 patients monitored for one to 11 years

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Abstract

Sulphasalazine is being used increasingly to treat rheumatoid arthritis, though its long term safety profile has not been established in this condition. The incidence and nature of adverse effects occurring in 774 patients with rheumatoid arthritis treated with sulphasalazine for periods ranging from one to 11 years were therefore noted. Altogether 205 of the patients stopped treatment permanently due to an adverse effect. One hundred and fifty six (76%) of these events occurred within three months and few beyond the first year. Most events were trivial and were self limiting after withdrawal of the drug; of the potentially more serious adverse effects, 33 (66%) occurred within three months of treatment. None of the patients died or suffered lasting ill effects.

It is concluded that adverse effects of treatment with sulphasalazine are generally seen within three months; though regular monitoring is desirable during that period, thereafter few worrying problems occur.

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Introduction

Several reports have suggested that sulphasalazine is a useful treatment for rheumatoid arthritis,[1-6] and the drug has been claimed to be safer than such alternatives as gold,[5,7] though this is disputed.[8] Any new treatment needs prolonged follow up of large numbers of patients so that its tolerability and serious toxicity can be estab-

lished. Three centres with extensive experience of treatment with sulphasalazine pooled experiences to establish its medium to long term toxicity when used in rheumatoid arthritis.

Patients and methods

The clinical records of all patients in three centres who started sulphasalazine for rheumatoid arthritis one year or more before the start of the study were examined. Follow up ranged from one to 11 years. Most patients had received enteric coated sulphasalazine. Treatment policy varied between the three centres, but all patients were usually aiming to take 1·5-3·0 g sulphasalazine daily according to need and tolerability. A few did not achieve 1·5 g and few exceeded 3·0 g. All definite or possible toxic events that led to permanent withdrawal of treatment were recorded and the time of withdrawal noted. Concurrent administration of adrenal corticosteroids was also noted. Table I shows the characteristics of the patients.

TABLE I—*Characteristics of patients*

	Birmingham	Glasgow	Sheffield	Total
No	324	158	292	774
No (%) of men	73 (23)	34 (22)	100 (34)	207 (27)
No (%) seropositive	254 (78)	138 (87)	223 (76)	615 (79)
Mean age (years) (range)	52·5 (16-84)	56·0 (28-79)	51·1 (11-78)	52·7 (11-84)
Mean duration of disease (years) (range)	7·5 (1-42)	10·6 (1-57)	5·1 (1-34)	7·1 (1-57)
No (%) taking corticosteroids	55 (17·0)	2 (1·3)	59 (20·2)	116 (15·0)

Only 15 patients were lost to follow up in the first year, and a further 16 were lost after the first year for reasons such as moving from the area, intercurrent unrelated illness, or simply a wish to stop attending the clinic. Efforts were made to ascertain that patients who had defaulted from follow up had not done so because of adverse effects.

TABLE II—*Toxic events leading to withdrawal of sulphasalazine. Figures are numbers of events (and percentages of all patients)*

	Birmingham	Glasgow	Sheffield	Total
Central and gastrointestinal	76 (23·4)	25 (15·8)	46 (15·8)	147 (19·0)
Mucocutaneous*	17 (5·2)	9 (5·7)	11 (3·8)	37 (4·8)
Haematological†:				
Leucopenia	1 (0·3)	7 (4·4)	0 (0)	8 (1·0)
Megaloblastic anaemia	1 (0·3)	0 (0)	0 (0)	1 (0·1)
Miscellaneous	6 (1·9)	3 (1·9)	3 (1·0)	12 (1·6)
Total	101 (31·2)	44 (27·8)	60 (20·5)	205 (26·5)

*Six additional patients with a rash were successfully desensitised and continued treatment.
†Three further episodes of leucopenia, five of megaloblastic anaemia, and one of thrombocytopenia were seen. Either the patients continued treatment or the drug was not withdrawn for these reasons.

The toxic events were classified into four groups as central and gastrointestinal, mucocutaneous, haematological, or miscellaneous as follows—central and gastrointestinal: nausea, vomiting, abdominal pain, headache, dizziness, lightheadedness, depression, irritability, sleep disturbance; mucocutaneous: rash, facial swelling, mouth ulcers; haematological: leucopenia, megaloblastic anaemia, thrombocytopenia; miscellaneous: flare of symptoms, dyspnoea, abnormal results of liver function tests, numb hands, urinary retention.

Results

Altogether 774 patients were reviewed; in 205 (26%) treatment was stopped permanently because of a possible toxic event (table II). A total of 383 (50%) stopped treatment within the first year of treatment: 199 did so because of toxicity and most of the remainder because of inefficacy of treatment, though a few felt much better, became pregnant, or were lost to follow up. Altogether 397 patients achieved one full year of treatment and 175 and 84 reached two and three years, respectively, with 11 years being the longest period of continuous treatment.

The commonest toxic events were nausea, vomiting, dizziness, and abdominal pain, which accounted for 125 (61%) of all withdrawals because of toxicity. It was sometimes difficult to decide whether the dominant symptoms were central or gastrointestinal, and these categories were thus considered together. It was usual for several of the above symptoms to occur together. Five patients had diarrhoea as the principal symptom. Disturbance of mood such as depression or irritability or, less specifically, a general feeling of unease accounted for 22 of the 147 patients with central or gastrointestinal symptoms.

Mucocutaneous reactions were the second commonest events, leading to withdrawal in 37 (5%) patients. Several distinct clinical types of rash were seen, the commonest being pruritic maculopapular generalised eruptions with no particular predilection for exposed skin; in some cases the rash was apparently due to photosensitivity of exposed areas including the lips, often occurring after a period of especially sunny weather. A few patients had urticarial lesions, sometimes accompanied by mild facial swelling. Two patients had mouth ulcers as the sole mucocutaneous manifestation. None of the patients had a typical Stevens-Johnson syndrome or toxic epidermal necrolysis.

Eight patients were withdrawn from treatment because of leucopenia (table III); seven of these events occurred in Glasgow, and in three of the eight the leucopenia was especially severe. Three further patients developed transient leucopenia but continued to take sulphasalazine. All 11 patients were women. Megaloblastic anaemia, usually in association with folic acid deficiency, was seen in six patients, though in only one was it the cause of withdrawal of the drug. Of the six patients, four had isolated folate deficiency, one had a low serum vitamin B12 concentration, and one had low concentrations of both vitamins. Although none of the patients stopped treatment because of thrombocytopenia, one developed severe thrombocytopenia three weeks after stopping sulphasalazine for another reason. The lowest recorded platelet count was 5×10^9/l; the patient recovered without sequelae when treated with prednisolone.

A small number of miscellaneous events were recorded, including an appreciable flare of arthritic symptoms in six, numb hands in one, and urinary retention in one. Two patients stopped the drug because of abnormal results of liver function tests, though one was jaundiced and subsequently shown to have gall stones; in the other liver biopsy showed a hepatitic picture with perivascular confluent necrosis and foci of liver cell necrosis. A third

TABLE III—*Details of patients who developed leucopenia while taking sulphasalazine*

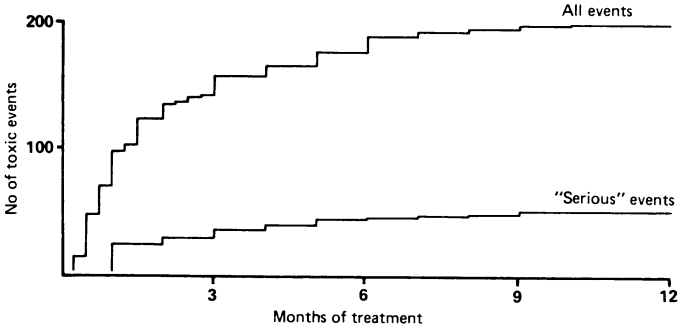
Case No	Age (years)	Sex	Rheumatoid factor	Dose of sulphasalazine (g/day) at diagnosis	Pretreatment white cell count ($\times10^9$/l)	Lowest white cell count ($\times10^9$/l)	% Neutrophils	Time of diagnosis from start of treatment (weeks)	Time to recovery (weeks)	Associated symptoms
1	64	F	+	1·5	8·1	1·1	10	5	3	Mouth ulcers, fever
2	70	F	+	3·0	9·8	0·5	NA	9	<1	Purulent tonsillitis
3	54	F	+	3·0	6·6	3·3	61	8	3	None
4	41	F	+	3·0	4·8	2·5	74	10	1	Perioral parasthesiae
5	67	F	+	3·0	6·5	2·2	26	2	3	None
6	43	F	+	1·5	3·4	2·6	38	4	2	None
7	41	F	+	1·5	5·0	3·8	NA	8	<1	None
8	44	F	+	1·5	8·0	1·4	6	4	1	None
9	*50	F	+	2·0	4·1	2·6	NA	25	2	None
10	*58	F	+	3·0	4·4	1·8	NA	233	2	None
11	*57	F	+	2·5	6·1	3·1	NA	8	†	None

NA=Not available.
*Patient recovered and continued to take same or reduced dose of sulphasalazine.
†White cell count remained at $3\text{-}4\times10^9$/l while patient took reduced dose of sulphasalazine for 15 months.

patient who stopped treatment with symptoms suggestive of gastrointestinal disturbance was found to have abnormal results of liver function tests and recovered spontaneously. No evidence of viral infection was found in these patients. Two patients became dyspnoeic after three and 35 weeks, respectively. In both the drug was withdrawn before return to hospital, by which time full recovery had taken place, and no further investigations were carried out.

The prevalence of concurrent administration of oral corticosteroids varied from two patients (1·3%) in Glasgow to 55 (17·0%) in Birmingham and 59 (20·2%) in Sheffield. This seemed to have little impact on the incidence of toxic events generally, though only one of the 11 patients who developed leucopenia was also receiving corticosteroids.

One hundred and twenty one (59%) of the 205 toxic events were recorded in the first six weeks of treatment and 156 (76%) within the first three months. The figure shows the timing of withdrawal because of toxicity in the first year of treatment. Of the potentially more serious adverse reactions (leucopenia, rash, abnormal results of liver function tests, dyspnoea), 33 (66%) were diagnosed in the first three months of treatment. All cases of leucopenia leading to permanent withdrawal of treatment occurred within this period.



Cumulative withdrawal from treatment with sulphasalazine during first year.

Only six patients withdrew from treatment because of possible adverse reactions after the first year; one had a rash and five suffered gastrointestinal symptoms. None of the 774 patients died or suffered lasting ill effects.

Discussion

Most toxic events were trivial, resolving rapidly when treatment was stopped. Nausea, dyspepsia, headache, dizziness, and abdominal pain often occurred together. Many of these symptoms are central in origin, relating to blood concentrations of sulphapyridine,[9] which, however, may be the active moiety in rheumatoid arthritis.[10,11] Most occurred early, and the need to withdraw treatment was reduced by routine use of enteric coated sulphasalazine, dose manipulation, and the short term use of antiemetics. Depression, irritability, and mood disturbances were not infrequent, occurring, with one exception, within the first six months. Cutaneous reactions of many types are recorded with sulphasalazine[12]; the less serious rashes may be managed by desensitisation, which allows treatment to be continued.[13]

Haematological abnormalities provided the one discrepancy between the experiences of the three centres; eight of the 11 cases of leucopenia were in Glasgow. The overall incidence of leucopenia (1·4%), however, was comparable with that seen in a group of 133 patients treated for inflammatory bowel disease (1·5%),[9] though in that study leucopenia occurred only in a subgroup of 34 very ill patients treated prospectively and no cases were seen in a larger group receiving maintenance treatment for inflammatory bowel disease. All 11 patients in the present series recovered spontaneously, and in one the drug was not withdrawn even temporarily. Leucopenia is most likely to occur in the first three months of treatment,[8,9,14] though in two of our patients it occurred after six and 54 months, respectively; both continued to take sulphasalazine with full recovery of the white cell count—this recovery has also been noted in inflammatory bowel disease.[9]

The reason for the large variation in the incidence of leucopenia between Birmingham, Sheffield, and Glasgow is unclear. It might be that transient falls in the white cell count take place with spontaneous recovery and are recognised more commonly in Glasgow, where the policy is to undertake much more regular haematological surveillance (every two weeks) than in Birmingham and Sheffield (every six to 12 weeks). Another possible explanation might be that the far greater prevalence of concurrent treatment with oral corticosteroids in Birmingham and Sheffield conferred some protection compared with Glasgow, where few patients received them. Whatever the reason, it seems fair to assume that profound leucopenia is a rare problem that usually occurs within three months.

Thrombocytopenia was encountered only once and was not a reason for stopping treatment; it has been anecdotally described in inflammatory bowel disease managed with sulphasalazine.[15] Megaloblastic anaemia was seen in six patients but was the prime reason for stopping treatment in only one; it occurred after five to 33 months of treatment.

Brittle folate state is known to occur in rheumatoid arthritis.[16-19] Sulphasalazine might exacerbate this, as it competitively inhibits absorption of folate from the intestine.[20,21] Folate deficient anaemia has been reported in a patient with colitis after six months' treatment.[22] Direct effects on red blood cells have also been noted,[23] with changes in cell morphology leading to premature haemolysis and therefore reticulocytosis and macrocytosis. Modest increases in red cell mean corpuscular volume commonly accompany treatment with sulphasalazine for rheumatoid arthritis, though decreases in serum folate concentrations are not usually observed.[23] Possibly a few patients with rheumatoid arthritis are stressed by sulphasalazine, either by malabsorption of folate or by haemolysis, to the point of frank megaloblastic anaemia with folate deficiency. This cannot be predicted by monitoring small increases in red cell mean corpuscular volume.

Dyspnoea due to sulphasalazine has been the subject of anecdotal reports and occurred twice in this series. It generally occurs within a few weeks and has been accompanied by infiltrations in chest *x* ray films, fever, and peripheral blood eosinophilia with or without a rash[24,25]; all patients have recovered. There is one report of fatal fibrosing alveolitis occurring four months after the introduction of sulphasalazine.[26] Hepatitic reactions seem to be rare when the drug is used for gastroenterological or rheumatological reasons. Increased enzyme activities usually occur in the first weeks of treatment accompanied by fever, rash, hepatomegaly, and possibly eosinophilia.[27-30] In one patient widespread non-caseating granulomas were present on liver biopsy.[27] Two patients with rheumatoid arthritis who developed raised alkaline phosphatase and aspartate transaminase activities during treatment with sulphasalazine have been reported.[31] Both recovered when treatment was stopped.

As with other second line antirheumatoid drugs, toxicity is a limiting factor in the use of sulphasalazine. Most of the toxic events, however, were trivial in their implications, and the type and incidence of events seem to differ little in patients with rheumatological and gastroenterological conditions. The drug has been widely used by gastroenterologists for many years and is regarded as generally safe and requiring little formal monitoring. As most potentially serious toxicity, and especially leucopenia, takes place early it seems sensible to be vigilant in the first three months. It is current practice in Birmingham and Sheffield to carry out a blood count monthly and to warn patients to report any worrying symptoms during the first three months. In Glasgow a fortnightly blood count is obtained. Beyond the first three months it is debatable whether formal monitoring is required; the policy adopted in Birmingham and Sheffield is to review patients according to clinical need and carry out blood counts at the time. In practice this means at intervals of several weeks to several months in the first year of treatment and less frequently subsequently if the patient remains well. In Glasgow, however, patients are seen every six weeks for the first year and every three months thereafter.

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SHORT REPORTS

Prevalence of known diabetes in an urban Indian environment: the Darya Ganj diabetes survey

A high prevalence of diabetes among migrant Indian Asians has been reported from several places, most recently from Southall, London.[1] The prevalence in India has not been found to be unduly high,[2] implying that the high prevalence in migrants may relate to newly encountered environmental factors. No large studies of prevalence have been performed in India in recent years. We therefore undertook a survey in New Delhi, using a protocol closely similar to that used in the Southall diabetes survey.

Methods and results

A house to house inquiry was made at all households within a defined area in Darya Ganj, a fairly affluent suburb of New Delhi. Residents were asked whether anyone living there was known to be diabetic. If the answer was yes a questionnaire, formulated as for the Southall diabetes survey, was completed.

Information was obtained on 6878 residents (3643 (53%) men and 3235 (47%) women). A total of 213 people were reported to be diabetic, giving an overall crude prevalence of 3·1%. The table shows the age distribution of the diabetics and the age specific prevalence of the disease. None of the diabetics reported were aged under 30; above this age the prevalence rose sharply to a peak of 16·9% in the age group 60-64. There were almost twice as many men (138) as women (75) with diabetes (crude prevalences of 3·8% and 2·3% respectively), and the age specific prevalence in men exceeded that in women at virtually all ages. All patients had been aged over 21 when diabetes was diagnosed, and 159 (75%) had been aged 30-54. Thirty five (16%) were treated with insulin and a further 150 (70%) received oral hypoglycaemic drugs. The mean known duration of diabetes was 8·4 years. Altogether 209 of the diabetics (98%) were Hindu and 154 (72%) vegetarian. One hundred and seventeen (85%) of the men with diabetes were businessmen and 97 (70%) graduates; the mean income of all the men with diabetes was 2500 rupees a month.

Prevalence of diabetes by age

Age (years)	Total population	No (%) with diabetes		
		Both sexes	Men	Women
30-34	555	7 (1·3)	5 (1·6)	2 (0·8)
35-39	546	10 (1·8)	5 (1·9)	5 (1·8)
40-44	437	18 (4·1)	9 (3·8)	9 (4·5)
45-49	415	32 (7·7)	25 (10·7)	7 (3·8)
50-54	374	32 (8·6)	20 (9·8)	12 (7·1)
55-59	300	27 (9·0)	16 (10·8)	11 (7·2)
60-64	266	45 (16·9)	30 (20·7)	15 (12·4)
65-69	154	18 (11·7)	10 (11·9)	8 (11·4)
70-74	109	14 (12·8)	10 (14·1)	4 (10·5)
75-79	47	7 (14·9)	5 (16·7)	2 (11·8)
80-84	28	2 (7·1)	2 (10·5)	
85+	22	1 (4·5)	1 (7·1)	

*No cases of diabetes were found in people aged under 30.

Comment

This survey showed an unexpectedly high prevalence of known diabetes in a fairly affluent population in New Delhi. The prevalence is much higher than that found in previous Indian surveys, although direct comparison is difficult owing to different methods of ascertainment. In a large study performed by the Indian Council of Medical Research in 1975 the total prevalence (of known and newly ascertained diabetes) in subjects aged over 15 in six urban centres ranged from 0·9% (Delhi) to 3·7% (Ahmedabad), with a mean of 2·1%.[2] About one half of the subjects were previously known diabetics. In Ahmedabad the prevalence of known diabetes was 1·65%,[3] compared with 4·1% in the same age group in this study.

The high prevalence in Darya Ganj may relate to socioeconomic state, improved relative survival of patients with diabetes, more intensive screening of the population, or all of these factors. Most subjects came from business or professional families, and the mean monthly income was considerably above the national average. Whatever the explanation, the reported prevalence was much higher than we had expected. Moreover, there were probably other people in the community with undiagnosed diabetes. The true prevalence can be ascertained only by systematically applying standard diagnostic techniques.[4] The age specific prevalences reported are strikingly similar to those found in Asians in Southall and at least five times as high as those in Europeans in Southall aged 40-64.[1] More complete diagnostic ascertainment would be unlikely to negate these major differences. Although Asians in Southall comprise mainly Punjabi Sikhs, the economic state of the Southall and Delhi samples is probably comparable. A high prevalence may therefore occur within India as well as in migrants elsewhere if the population is exposed to appropriate environmental factors. Indian people would seem to rank high in terms of ethnic susceptibility to diabetes.

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